IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#8

In re	:	U.S. Patent No. 4,376,858
Issued	:	March 15, 1983
Patentee	:	Norman L. Colbry
For	:	2-4-DIAMINO-5-METHYL-6-[(3,4,5-TRIMETHOXY-ANILINO)METHYL]QUINAZOLINE SALTS

BOX: PATENT TERM EXTENSION
Commissioner of Patents and Trademarks
Washington, D.C. 20231

TRANSMITTAL OF AN APPLICATION

FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Sir:

Transmitted herewith is an APPLICATION FOR EXTENSION OF PATENT TERM (an original and a certified duplicate original with declaration and attachments thereto) of the above-captioned patent for a product approved on December 17, 1993.

[X] The APPLICATION FOR EXTENSION OF PATENT TERM is being hand-carried to the U.S. Patent and Trademark Office.

[X] A prescribed fee in the amount of $1,000.00 is required for the application presented.
Please charge Deposit Account No. 23-0450 in the amount of the prescribed fee above, or such greater or lesser amount of excess fees for claims as the Commissioner determines is required by law. This letter is submitted in triplicate for deposit account purposes.

[X] Three (3) working copies of the APPLICATION FOR EXTENSION OF PATENT TERM and attachments to each are provided for the convenience of the U.S. Patent and Trademark Office.

Respectfully submitted,

FEBRUARY 7, 1994
Date

FRANCIS J. FINNEY,
Registration No. 33,069
Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105
Tel. (313) 996-7295

Attachments:

[X] An original APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156 with Declaration and attachments thereto.

[X] A certified duplicate original APPLICATION FOR EXTENSION OF PATENT TERM with Declaration and attachments thereto.

[X] Three (3) working copies of APPLICATION FOR EXTENSION OF PATENT TERM with Declaration and attachments thereto.

[X] This Transmittal Form (TERMEX.TRS) in triplicate for deposit account purposes.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	U.S. Patent No. 4,376,858	
Patentee:	Norman L. Colbry	**Box: Patent Term Extension**
Issue Date:	March 15, 1983	

REQUEST FOR EXTENSION OF PATENT TERM

UNDER 35 U.S.C. §156

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

Pursuant to §201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. §156, WARNER-LAMBERT COMPANY, of 201 Tabor Road, Morris Plains, New Jersey, 07950, assignee of the above- identified patent by an assignment from the inventor to WARNER-LAMBERT COMPANY, recorded August 19, 1981, at Reel 3887, Frames 362-363, hereby requests an extension of the patent term of United States Patent No. 4,376,858.

The following information is submitted in accordance with 35 U.S.C. §156(d) and 37 C.F.R. §1.740, and follows the numerical format set forth in 37 C.F.R. §1.740.

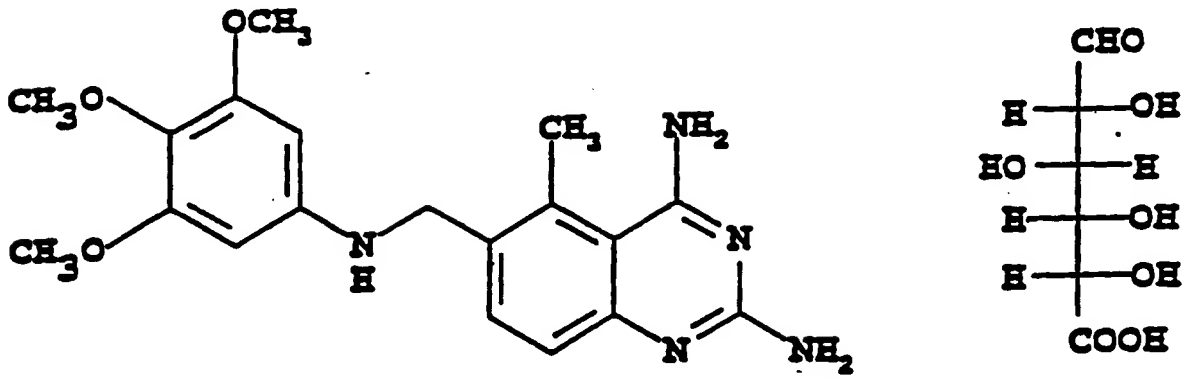
(1) A complete identification of the approved product by appropriate chemical and generic name, physical structure characteristics:

The approved product is NEUTREXIN™ (generic name - trimetrexate glucuronate). The active ingredient in NEUTREXIN™ is trimetrexate glucuronate. NEUTREXIN™ is for administration by injection.

Chemically it is 2,4-diamino-5-methyl-6[(3,4,5-trimethoxyanilino)methyl]quinazoline mono-D-glucuronate.

The name CI-898 is the internal name used by WARNER LAMBERT COMPANY.

Trimetrexate glucuronate has the following structural formula:



the empirical formula is $C_{19}H_{23}N_5O_3 \cdot C_6H_{10}O_7$
molecular weight is 563.56
369.42 (free base)

As noted above, NEUTREXIN™ contains trimetrexate glucuronate for injection; see the sections entitled DESCRIPTION and DOSAGE and ADMINISTRATION in Exhibit 1 (PACKAGE INSERT) which is the Product Information sheet for the approved product.

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred:

The regulatory review occurred under §505(b) of the Federal Food, Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. §301 et seq. Section 505 provides for the submission and approval of new drug applications ("NDAs") for products.

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred:

NEUTREXIN™ (trimetrexate glucuronate for injection) was approved by the Food and Drug Administration ("FDA") for commercial marketing pursuant to §505(b) of the FFDCA on December 17, 1993; see Exhibit 2 (APPROVAL LETTER).*

(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved and the provision of law under which it was approved.

The only active ingredient in NEUTREXIN™ (trimetrexate glucuronate for injection) is trimetrexate glucuronate. Trimetrexate glucuronate has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act.

* Material not relevant to the Application For Extension of Patent Term Under 35 U.S.C. §156 has been deleted.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to §1.720(f) and an identification of the date of the last day on which the application could be submitted.

The product was approved for commercial marketing on December 17, 1993, and the last day within the sixty day period permitted for submission of an application for extension of the patent term is February 14, 1994. The date of submission of the present application is no later than February 14, 1994, and therefore, the present application has been timely filed.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration:

Name of Inventor:	Norman L. Colbry
U.S. PATENT NO.	4,376,858
Issue Date:	March 15, 1983
Date of Original Expiration:	March 15, 2000

(7) A copy of the patent for which an extension is being sought including the entire specification (including claims) and drawings:

A copy of U.S. Patent 4,376,858 is attached as Exhibit 3 (PATENT).

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or re-examination certificate issued in the patent:

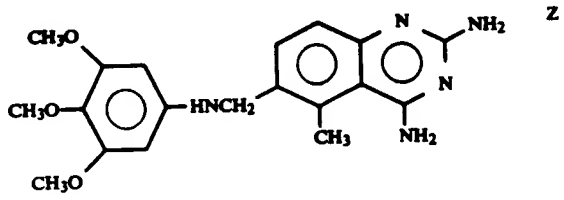
No disclaimer, certificate of correction or re-examination certificate has been issued. Copies of the receipts of the first and second maintenance fee payments paid by applicant are attached hereto as Exhibit 4. Said receipts have mailing dates of respectively, June 25, 1986 and September 12, 1990.

(9) A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product or a method of using or manufacturing the approved product:

U.S. Patent 4,376,858 ("'858") claims the approved product. The approved product NEUTREXIN™ (trimetrexate glucuronate by injection), known by the chemical name 2,4-diamino-5-methyl-6[(3,4,5-trimethoxyanilino)methyl]-quinazoline mono-D-glucuronate as described in item (1) hereof, is claimed in Claims 1, 3 and 5 of the '858 patent. In Claim 1 when Z represents glucuronic acid, the generic claim reads on the approved product 2,4-diamino-5-methyl-6[(3,4,5-trimethoxyanilino)methyl]quinazoline glucuronate.

Claim 1

A compound of the formula:



wherein Z is 2-hydroxyethanesulfonic acid or glucuronic acid.

Claim 3

The compound of claim 1 having the name 2,4-diamino-5-methyl-6-[(3,4,5-trimethoxyanilino)methyl]quinazoline glucuronate.

Claim 5

The compound of Claim 3 being in powdery form.

(10) A statement beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. §156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period as follows:

> **(i) For a patent claiming a human drug, antibiotic or human biological product, the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) was initially submitted and the NDA number and the date on which the NDA was approved:**

WARNER-LAMBERT COMPANY, in conjunction with the National Institute of Allergy & Infectious Diseases (NIAID) initiated the development of Neutrexin™ to establish safety and efficacy of the product. The development of the product was transferred to U.S.. Bioscience on November 15, 1991 who established Neutrexin™ (trimetrexate glucuronate for injection) with concurrent leucovorin administration (leucovorin protection) as an alternative therapy for the treatment of moderate-to-severe *Pneumocystis carinii* pneumonia (PCP) in immunocompromised patients, including patients with the acquired immunodeficiency syndrome (AIDS), who are intolerant of, or are refractory to, trimethoprim-sulfamethoxazole therapy or for whom trimethoprim-sulfamethoxazole is contraindicated.

On March 9, 1987, Parke-Davis Pharmaceutical Research Division of WARNER-LAMBERT COMPANY, the patent owner, submitted to the Food and Drug Administration ("FDA") a "Notice of Claimed Investigational Exemption for a New Drug" (hereinafter referred to as an "IND") for CI-898 trimetrexate glucuronate for injection. A copy of this letter is submitted herewith as Exhibit 5 (IND SUBMISSION LETTER).

The IND was assigned number 29,796. The IND became effective on September 2, 1987. See Exhibit 6 (Memo from T.N.T. Olson titled "Phone Call From Mr. James D. Bona (301/443-6797) Regarding the Clinical Hold on the Clinical Study with Trimetrexate for Pneumocystis"# and memo from J.E. Meisenhelder titled "FDA APPROVAL OF THE NIAID P.CARINNI CLINICAL STUDY") attached hereto. This establishes the beginning of the "regulatory review period" under 35 U.S.C.§156(g)(1) as September 2, 1987.

On February 1, 1993, a new drug application (NDA 20,326) was initially submitted by U.S. BIOSCIENCE under §505(b) of the Federal Food, Drug, and Cosmetic Act (FFDCA) for NEUTREXIN™ (trimetrexate glucuronate for injection). A copy of the cover letter of February 1, 1993, is submitted herewith as Exhibit 7 (NDA SUBMISSION LETTER).*

This NDA was approved on December 17, 1993. Attached as Exhibit 2 (APPROVAL LETTER) is a copy of a letter dated December 17, 1993, from the FDA to U.S. BIOSCIENCE approving the NDA for NEUTREXIN™ (trimetrexate glucuronate for injection).

Thus, for the purposes of determining the "regulatory review period" under 35 U.S.C. §156(g)(1), December 17, 1993, is the date of the first approval of trimetrexate glucuronate, which is the active ingredient in NEUTREXIN™.

"Trimetrexate (CI-898) IND 23-269 File" refers to another IND for trimetrexate originally held by Warner-Lambert and now held by U.S. Bioscience.

* Material not relevant to the Application For Extension of Patent Term Under 35 U.S.C. §156 has been deleted.

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities:

As described above in item (10), WARNER-LAMBERT COMPANY submitted an IND for trimetrexate glucuronate on March 9, 1987, which became effective on September 2, 1987, and, in close consultation with FDA, subsequently conducted clinical studies under this IND. The IND activity is summarized in the attached Exhibit 8 (IND LOG)* titled "REGULATORY LIAISON AND COMPLIANCE MANAGEMENT SYSTEM CI NUMBER 898 APPLICATION NUMBER=29,796." These activities were used to support the new drug application submitted by U.S. BIOSCIENCE on February 1, 1993.

Subsequent to the submission of this NDA, U.S. BIOSCIENCE had numerous contacts and meetings with the FDA with respect to the application and these are summarized in the attached Exhibit 9, (NDA LOG) NDA 20,326.

* Material not relevant to the Application For Extension of Patent Term Under 35 U.S.C. §156 has been deleted.

(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined:

Statement of Eligibility of the Patent for Extension Under 35 U.S.C. §156(a) and (c)(4)

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted, (2) the term of the patent has never been extended, (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. §156(d), (4) the product has been subject to a regulatory review period before its commercial marketing or use, and (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred; and §156(c)(4) provides, that in no event shall more than one patent be extended for the same regulatory review period for any product.

As described by corresponding number, each of these elements is satisfied here:

(1) The term of U.S. Patent No. 4,376,858 expires on March 15, 2000. This application has, therefore, been submitted before the expiration of the patent term. In addition, maintenance fees have been timely paid.

(2) The term of this patent has never been extended.

(3) This application is submitted by the owner of record, WARNER-LAMBERT COMPANY, (Assignment recorded on August 19, 1981, at Reel 3887, Frames 362-363). This application is submitted in accordance with 35 U.S.C. §156(d) in that it is submitted within the sixty-day period beginning on the date, December 17, 1993, that the product received permission for marketing under the Federal Food, Drug and Cosmetic Act and contains the information required under 35 U.S.C. §156(d).

(4) As evidenced by the December 17, 1993, letter from the FDA, Exhibit 2, (APPROVAL LETTER) the product was subject to a regulatory review period under §505(b)(1) of the FFDCA before its commercial marketing or use.

(5) The permission for the commercial marketing of NEUTREXIN™ (trimetrexate glucuronate for injection) after regulatory review under §505(b)(1) is the first permitted commercial marketing of trimetrexate glucuronate. This is confirmed by the absence of any approved new drug application under which trimetrexate glucuronate could be commercially marketed prior to December 17, 1993.

(6) No other patent has been extended for the same regulatory period for the approved product (§156(c)(4)).

Statement as to Length of Extension Claimed
In Accordance With 37 C.F.R. §1.775

The term of U.S. Patent No. 4,376,858 should be extended for a period of 1310 days to October 16, 2003.

The period of extension is determined in accordance with 35 U.S.C. §156 and follows the format set forth in 37 CFR §1.775(c) and (d).

37 CFR §1.775(c) The length of the regulatory review period for a human drug, antibiotic drug or human biological product will be determined by the Secretary of Health and Human Services. Under 35 U.S.C. 156(g)(1)(B), it is the sum of --

(1) The number of days in the period beginning on the date an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, and Cosmetic Act became effective for the approved product and ending on the date the application was initially submitted for such product under those sections or under section 351 of the public Health Service Act;

The number of days between the effective date of the initial IND, September 2, 1987, and the initial submission of the NDA, February 1, 1993, is a period of 1980 days

and

(2) The number of days in the period beginning on the date the application was initially submitted for the approved product under section 351 of the Public Health Service Act, subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act and ending on the date such application was approved under such section.

The number of days between the initial submission of the NDA, February 1, 1993, to NDA approval, December 17, 1993, is a period of 320 days.

37 C.F.R. §1.775(d) The term of the patent as extended for a human drug, antibiotic drug or human biological product will be determined by--

(1) Subtracting from the number of days determined by the Secretary of Health and Human Services to be in the regulatory review period:

(i) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section which were on and before the date on which the patent issued;

The number of days in the period of the IND, effective on September 2, 1987, which were on or before March 15, 1983, the date the patent was issued, is a period of 0 days,

1980 days minus 0 days equals 1980 days,

and

the number of days in the period of the NDA, effective on February 1, 1993, which were on or before March 15, 1983, the date the patent was issued, is a period of 0 days,

320 days minus 0 days equals 320 days.

(ii) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section during which it is determined under 35 U.S.C. §156(d)(2)(B) by the Secretary of Health and Human Services that applicant did not act with due diligence;

The number of days the applicant did not act with due diligence is 0 days,

therefore,

1980 days minus 0 days equals 1980 days.

320 days minus 0 days equals 320 days.

(iii) One-half the number of days remaining in the period defined by paragraph (c)(1) of this section after that period is reduced in accordance with paragraphs (d)(1)(i) and (ii) of this section; half days will be ignored for purposes of subtraction;

One-half of 1980 days equals 990 days.

Thus U.S. Patent No. 4,376,858 should be entitled to an extension of 1310 days (990 days plus 320 days).

(2) By adding the number of days determined in paragraph (d)(1) of this section to the original term of the patent as shortened by any terminal disclaimer;

Adding 1310 days to March 15, 2000,
the original term of the patent (no terminal disclaimer was made),
extends the term to October 16, 2003.

(3) By adding 14 years to the date of approval of the application under section 351 of the Public Health Service Act, or subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act;

Adding 14 years to December 17, 1993,
the date of approval of the application,
gives the date of December 17, 2007.

(4) By comparing the dates for the ends of the periods obtained pursuant to paragraphs (d)(2) and (d)(3) of this section with each other and selecting the earlier date;

The earlier date is October 16, 2003.

(5) If the original patent was issued after September 24, 1984,

This is not applicable for the patent.

(6) If the original patent was issued before September 24, 1984, and

(i) If no request was submitted for an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, and Cosmetic Act before September 24, 1984, by--

(A) Adding 5 years to the original expiration date of the patent or earlier date set by terminal disclaimer; and

Adding 5 years to March 15, 2000, the original expiration date of the patent, gives the date of March 15, 2005.

(B) By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(6)(i)(A) of this section with each other and selecting the earlier date;

The earlier date is October 16, 2003.

(ii) If a request was submitted for an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, or Cosmetic Act before September 24, 1984 and the commercial marketing or use of the product was not approved before September 24, 1984, by--

This is not applicable for the patent.

(13) A statement that applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought (see §1.765);

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and to the Secretary of Health and Human Services under 37 C.F.R. §1.765 any information which is material to the determination of the entitlement to the extension sought herein.

Applicant is unaware of any additional information material to this Application for Extension of Patent Term.

(14) Prescribed Fee:

The prescribed fee of $1,000.00 for receiving and acting on this application for extension of patent term is hereby authorized. Please charge Deposit Account No. 23-0450 in the amount of the fee above, or such greater or lesser amount of excess fees as the Commissioner determines is required by law.

(15) The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed:

Francis J. Tinney
Registration No. 33,069
Patent Department
WARNER-LAMBERT COMPANY
2800 Plymouth Road
Ann Arbor, Michigan 48105
Telephone: (313) 996-7295

(16) A duplicate of the application papers, certified as such.

A duplicate of the application papers, certified as such, is submitted herewith.

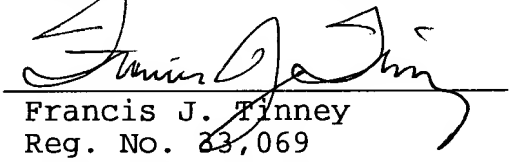
(17) An oath or Declaration as set forth in paragraph (b) of 37 C.F.R. §1.740.

DECLARATION

The undersigned is authorized to obligate WARNER-LAMBERT COMPANY, the owner of record of U.S. Patent 4,376,858, which has applied for an extension of term of this patent, I declare that, I have reviewed and understand the contents of this application being submitted pursuant to this section; that I believe that the patent is subject to extension pursuant to 37 C.F.R. §1.710; that I believe that the length of extension claimed is fully justified under 35 U.S.C. §156 and the applicable regulations; and that I believe that the patent for which this extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. §1.720.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application and any extension of U.S. Patent No. 4,376,858.

WARNER-LAMBERT COMPANY

By: 

Francis J. Tinney
Reg. No. 33,069
Assistant Secretary
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2800 Plymouth Road
Ann Arbor, Michigan 48105
(313) 996-7295

Date: FEBRUARY 7, 1994

FT1S3148.WP

NEUTREXIN™
(trimetrexate glucuronate for injection)

BIOSCIENCE

LB3003 PA

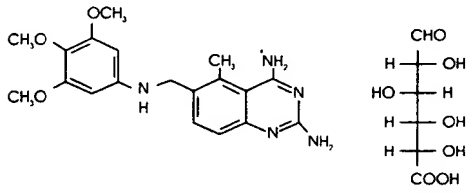
WARNINGS

NEUTREXIN (TRIMETREXATE GLUCURONATE FOR INJECTION) MUST BE USED WITH CONCURRENT LEUCOVORIN (LEUCOVORIN PROTECTION) TO AVOID POTENTIALLY SERIOUS OR LIFE-THREATENING TOXICITIES (SEE PRECAUTIONS AND DOSAGE AND ADMINISTRATION).

DESCRIPTION

Neutrexin is the brand name for trimetrexate glucuronate. Trimetrexate, a 2,4-diaminoquinazoline, non-classical folate antagonist, is a synthetic inhibitor of the enzyme dihydrofolate reductase (DHFR). Neutrexin is available as a sterile lyophilized powder in single-dose vials, each containing 25 mg of trimetrexate and 15 mg of D-glucuronic acid (40 mg of trimetrexate glucuronate) without any preservatives or excipients. The powder is reconstituted prior to intravenous infusion (see **DOSAGE AND ADMINISTRATION, RECONSTITUTION AND DILUTION**).

Trimetrexate glucuronate is chemically known as 2,4-diamino-5-methyl-6-[(3,4,5-trimethoxyanilino)methyl] quinazoline mono-D-glucuronate, and has the following structure:



The empirical formula for trimetrexate glucuronate is $C_{19}H_{23}N_5O_3 \cdot C_6H_{10}O_7$ with a molecular weight of 563.56. The active ingredient, trimetrexate free base, has an empirical formula of $C_{19}H_{23}N_5O_3$ with a molecular weight of 369.42. Trimetrexate glucuronate for injection is a pale greenish-yellow powder or cake. Trimetrexate glucuronate is soluble in water (>50 mg/mL), whereas trimetrexate free base is practically insoluble in water (<0.1 mg/mL). The pKa of trimetrexate free base in 50% methanol/water is 8.0. The logarithm$_{10}$ of the partition coefficient of trimetrexate free base between octanol and water is 1.63.

CLINICAL PHARMACOLOGY

Mechanism of Action

In vitro studies have shown that trimetrexate is a competitive inhibitor of dihydrofolate reductase (DHFR) from bacterial, protozoan, and mammalian sources. DHFR catalyzes the reduction of intracellular dihydrofolate to the active coenzyme tetrahydrofolate. Inhibition of DHFR results in the depletion of this coenzyme, leading directly to interference with thymidylate biosynthesis, as well as inhibition of folate-dependent formyltransferases, and indirectly to inhibition of purine biosynthesis. The end result is disruption of DNA, RNA, and protein synthesis, with consequent cell death.

Leucovorin (folinic acid) is readily transported into mammalian cells by an active, carrier-mediated process and can be assimilated into cellular folate pools following its metabolism. *In vitro* studies have shown that leucovorin provides a source of reduced folates necessary for normal cellular biosynthetic processes. Because the *Pneumocystis carinii* organism lacks the reduced folate carrier-mediated transport system, leucovorin is prevented from entering the organism. Therefore, at concentrations achieved with therapeutic doses of trimetrexate plus leucovorin, the selective transport of trimetrexate, but not leucovorin, into the *Pneumocystis carinii* organism allows the concurrent administration of leucovorin to protect normal host cells from the cytotoxicity of trimetrexate without inhibiting the antifolate's inhibition of *Pneumocystis carinii*. It is not known if considerably higher doses of leucovorin would affect trimetrexate's effect on *Pneumocystis carinii*.

Microbiology

Trimetrexate inhibits, in a dose-related manner, *in vitro* growth of the trophozoite stage of rat *Pneumocystis carinii* cultured on human embryonic lung fibroblast cells. Trimetrexate concentrations between 3 and 54.1 µM were shown to inhibit the growth of trophozoites. Leucovorin alone at a concentration of 10 µM did not alter either the growth of the trophozoites or the anti-pneumocystis activity of trimetrexate. Resistance to trimetrexate's antimicrobial activity against *Pneumocystis carinii* has not been studied.

Pharmacokinetics

Trimetrexate pharmacokinetics were assessed in six patients with acquired immunodeficiency syndrome (AIDS) who had *Pneumocystis carinii* pneumonia (4 patients) or toxoplasmosis (2 patients). Trimetrexate was administered intravenously as a bolus injection at a dose of 30 mg/m²/day along with leucovorin 20 mg/m² every 6 hours for 21 days. Trimetrexate clearance (mean ± SD) was 38 ± 15 mL/min/m² and volume of distribution at steady state (Vd_{SS}) was 20 ± 8 L/m². The plasma concentration time profile declined in a biphasic manner over 24 hours with a terminal half-life of 11 ± 4 hours.

The pharmacokinetics of trimetrexate without the concomitant administration of leucovorin have been evaluated in cancer patients with advanced solid tumors using various dosage regimens. The decline in plasma concentrations over time has been described by either biexponential or triexponential equations. Following the single-dose administration of 10 to 130 mg/m² to 37 patients, plasma concentrations were obtained for 72 hours. Nine plasma concentration time profiles were described as biexponential. The alpha phase half-life was 57 ± 28 minutes, followed by a terminal phase with a half-life of 16 ± 3 hours. The plasma concentrations in the remaining patients exhibited a triphasic decline with half-lives of 8.6 ± 6.5 minutes, 2.4 ± 1.3 hours, and 17.8 ± 8.2 hours.

Trimetrexate clearance in cancer patients has been reported as 53 ± 41 mL/min (14 patients) and 32 ± 18 mL/min/m² (23 patients) following single-dose administration. After a five-day infusion of trimetrexate to 16 patients, plasma clearance was 30 ± 8 mL/min/m².

Renal clearance of trimetrexate in cancer patients has varied from about 4 ± 2 mL/min/m² to 10 ± 6 mL/min/m². Ten to 30% of the administered dose is excreted unchanged in the urine. Considering the free fraction of trimetrexate, active tubular secretion may possibly contribute to the renal clearance of trimetrexate. Renal clearance has been associated with urine flow, suggesting the possibility of tubular reabsorption as well.

The Vd_{SS} of trimetrexate in cancer patients after single-dose administration and for whom plasma concentrations were obtained for 72 hours was 36.9 ± 17.6 L/m² (n=23) and 0.62 ± 0.24 L/kg (n=14). Following a constant infusion of trimetrexate for five days, Vd_{SS} was 32.8 ± 16.6 L/m². The volume of the central compartment has been estimated as 0.17 ± 0.08 L/kg and 4.0 ± 2.9 L/m².

There have been inconsistencies in the reporting of trimetrexate protein binding. The *in vitro* plasma protein binding of trimetrexate using ultrafiltration is approximately 95% over the concentration range of 18.75 to 1000 ng/mL. There is a suggestion of capacity limited binding (saturable binding) at concentrations greater than about 1000 ng/mL, with free fraction progressively increasing to about 9.3% as concentration is increased to 15 µg/mL. Other reports have declared trimetrexate to be greater than 98% bound at concentrations of 0.1 to 10 µg/mL; however, specific free fractions were not stated. The free fraction of trimetrexate also has been reported to be about 15 to 16% at a concentration of 60 ng/mL, increasing to about 20% at a trimetrexate concentration of 6 µg/mL.

Trimetrexate metabolism in man has not been characterized. Preclinical data strongly suggest that the major metabolic pathway is oxidative O-demethylation, followed by conjugation to either glucuronide or the sulfate. N-demethylation and oxidation is a related minor pathway. Preliminary findings in humans indicate the presence of a glucuronide conjugate with DHFR inhibition and a demethylated metabolite in urine.

The presence of metabolite(s) in human plasma following the administration of trimetrexate is suggested by the differences seen in trimetrexate plasma concentrations when measured by HPLC and a nonspecific DHFR inhibition assay. The profiles are similar initially, but diverge with time; concentrations determined by DHFR being higher than those determined by HPLC. This suggests the presence of one or more metabolites with DHFR inhibition activity. After intravenous administration of trimetrexate to humans, urinary recovery averaged about 40%, using a DHFR assay, in comparison to 10% urinary recovery as determined by HPLC, suggesting the presence of one or more metabolites that retain inhibitory activity against DHFR. Fecal recovery of trimetrexate over 48 hours after intravenous administration ranged from 0.09 to 7.6% of the dose as determined by DHFR inhibition and 0.02 to 5.2% of the dose as determined by HPLC.

The pharmacokinetics of trimetrexate have not been determined in patients with renal insufficiency or hepatic dysfunction.

Exhibit 1

INDICATIONS AND USAGE

Neutrexin (trimetrexate glucuronate for injection) with concurrent leucovorin administration (leucovorin protection) is indicated as an alternative therapy for the treatment of moderate-to-severe *Pneumocystis carinii* pneumonia (PCP) in immunocompromised patients, including patients with the acquired immunodeficiency syndrome (AIDS), who are intolerant of, or are refractory to, trimethoprim-sulfamethoxazole therapy or for whom trimethoprim-sulfamethoxazole is contraindicated.

This indication is based on the results of a randomized, controlled double-blind trial comparing Neutrexin with concurrent leucovorin protection (TMTX/LV) to trimethoprim-sulfamethoxazole (TMP/SMX) in patients with moderate-to-severe *Pneumocystis carinii* pneumonia, as well as results of a Treatment IND. These studies are summarized below:

Neutrexin Comparative Study with TMP/SMX: This double-blind, randomized trial initiated by the AIDS Clinical Trials Group (ACTG) in 1988 was designed to compare the safety and efficacy of TMTX/LV to that of TMP/SMX for the treatment of histologically confirmed, moderate-to-severe PCP, defined as (A-a) baseline gradient >30 mmHg, in patients with AIDS.

Of the 220 patients with histologically confirmed PCP, 109 were randomized to receive TMTX/LV and 111 to TMP/SMX. Study patients randomized to TMTX/LV treatment were to receive 45 mg/m² of TMTX daily for 21 days plus 20 mg/m² of LV every 6 hours for 24 days. Those randomized to TMP/SMX were to receive 5 mg/kg TMP plus 25 mg/kg SMX four times daily for 21 days.

Response to therapy, defined as alive and off ventilatory support at completion of therapy, without a requirement for a change in anti-pneumocystis therapy, or addition of supraphysiologic doses of steroids, occurred in fifty percent of patients in each treatment group.

The observed mortality in the TMTX/LV treatment group was approximately twice that in the TMP/SMX treatment group (95% CI: 0.99 - 4.11). Thirty of 109 (27%) patients treated with TMTX/LV and 18 of 111 (16%) patients receiving TMP/SMX died during the 21-day treatment course or 4-week follow-up period. Twenty-seven of 30 deaths in the TMTX/LV arm were attributed to PCP; all 18 deaths in the TMP/SMX arm were attributed to PCP.

A significantly smaller proportion of patients who received TMTX/LV compared to TMP/SMX failed therapy due to toxicity (10% vs. 25%), and a significantly greater proportion of patients failed due to lack of efficacy (40% vs. 24%). Six patients (12%) who responded to TMTX/LV relapsed during the one-month follow-up period; no patient responding to TMP/SMX relapsed during this period. Information is not available as to whether these patients received prophylaxis therapy for PCP.

Treatment IND: The FDA granted a Treatment IND for Neutrexin with leucovorin protection in February 1988 to make Neutrexin therapy available to HIV-infected patients with histologically confirmed PCP who had disease refractory to or who were intolerant of TMP/SMX and/or intravenous pentamidine.

Over 500 physicians in the United States participated in the Treatment IND. As of January 15, 1992, a total of 753 patients had been enrolled of whom 577 were evaluable for efficacy. Of the 577 evaluable patients, 227 patients were intolerant of both TMP/SMX and pentamidine (IST - patients intolerant of both standard therapies), 146 were intolerant of one therapy and refractory to the other (RIST - patients refractory to one therapy and intolerant of the other) and 204 were refractory to both therapies (RST - refractory to both standard therapies). This was a very ill patient population; 38% required ventilatory support at entry (Table 1). These studies did not have concurrent control groups.

TABLE 1
TREATMENT IND
Baseline Characteristics

	IST (n=227)	RIST (n=146)	RST (n=204)	TOTAL (n=577)
Ventilatory Support Required n (%)	39 (17)	50 (34)	129 (63)	218 (38)
Median Days on Standard Therapy	10	12	16	14
First Episode of PCP n (%)	104 (46)	103 (71)	190 (93)	397 (69)

The overall survival rate one month after completion of TMTX/LV as salvage therapy was 48%. Patients who had not responded to treatment with both TMP/SMX and pentamidine, of whom 63% required mechanical ventilation at entry, achieved a survival rate of 25% following treatment with TMTX/LV. Survival was 67% in patients who were intolerant to both TMP/SMX and pentamidine (Table 2).

TABLE 2
TREATMENT IND
Survival Rate One Month After Completion of Neutrexin Therapy

	IST	RIST	RST
All Patients	153/227 (67%)	73/146 (50%)	50/204 (25%)
Baseline Ventilatory Support	9/39 (23%)	15/50 (30%)	18/129 (14%)
No Baseline Ventilatory Support	144/188 (77%)	58/96 (60%)	32/75 (43%)

In the Treatment IND, 12% of the patients discontinued Neutrexin therapy (with leucovorin protection) for toxicity.

CONTRAINDICATIONS

Neutrexin (trimetrexate glucuronate for injection) is contraindicated in patients with clinically significant sensitivity to trimetrexate, leucovorin, or methotrexate.

WARNINGS

Neutrexin (trimetrexate glucuronate for injection) must be used with concurrent leucovorin to avoid potentially serious or life-threatening complications including bone marrow suppression, oral and gastrointestinal mucosal ulceration, and renal and hepatic dysfunction. Leucovorin therapy must extend for 72 hours past the last dose of Neutrexin. Patients should be informed that failure to take the recommended dose and duration of leucovorin can lead to fatal toxicity. Patients should be closely monitored for the development of serious hematologic adverse reactions (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Neutrexin can cause fetal harm when administered to a pregnant woman. Trimetrexate has been shown to be fetotoxic and teratogenic in rats and rabbits. Rats administered 1.5 and 2.5 mg/kg/day intravenously on gestational days 6-15 showed substantial postimplantation loss and severe inhibition of maternal weight gain. Trimetrexate administered intravenously to rats at 0.5 and 1.0 mg/kg/day on gestational days 6-15 retarded normal fetal development and was teratogenic. Rabbits administered trimetrexate intravenously at daily doses of 2.5 and 5.0 mg/kg/day on gestational days 6-18 resulted in significant maternal and fetotoxicity. In rabbits, trimetrexate at 0.1 mg/kg/day was teratogenic in the absence of significant maternal toxicity. These effects were observed using doses 1/20 to 1/2 the equivalent human therapeutic dose based on a mg/m² basis. Teratogenic effects included skeletal, visceral, ocular, and cardiovascular abnormalities. If Neutrexin is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

General

Patients receiving Neutrexin (trimetrexate glucuronate for injection) may experience severe hematologic, hepatic, renal, and gastrointestinal toxicities. Caution should be used in treating patients with impaired hematologic, renal, or hepatic function. Patients who require concomitant therapy with nephrotoxic, myelosuppressive, or hepatotoxic drugs should be treated with Neutrexin at the discretion of the physician and monitored carefully. To allow for full therapeutic doses of Neutrexin, treatment with zidovudine should be discontinued during Neutrexin therapy.

Neutrexin-associated myelosuppression, stomatitis, and gastrointestinal toxicities can generally be ameliorated by adjusting the dose of leucovorin. Mild elevations in transaminases and alkaline phosphatase have been observed with Neutrexin administration and are usually not cause for modification of Neutrexin therapy (see **DOSAGE AND ADMINISTRATION**). Seizures have been reported rarely (< 1%) in AIDS patients receiving Neutrexin; however, a causal relationship has not been established. An anaphylactoid reaction has been reported in a cancer patient receiving Neutrexin as a bolus injection.

Neutrexin has not been evaluated clinically for the treatment of concurrent pulmonary conditions such as bacterial, viral, or fungal pneumonia or mycobacterial diseases. *In vitro* activity has been observed against *Toxoplasma gondii*, *Mycobacterium avium* complex, gram positive cocci, and gram negative rods. If clinical deterioration is observed in patients, they should be carefully evaluated for other possible causes of pulmonary disease and treated with additional agents as appropriate.

Laboratory Tests

Patients receiving Neutrexin with leucovorin protection should be seen frequently by a physician. Blood tests to assess the following parameters should be performed at least twice a week during therapy: hematology (absolute neutrophil counts [ANC], platelets), renal function (serum creatinine, BUN), and hepatic function (SGOT, SGPT, alkaline phosphatase).

Drug Interactions

Since trimetrexate is metabolized by a P450 enzyme system, drugs that induce or inhibit this drug metabolizing enzyme system may elicit important drug-drug interactions that may alter trimetrexate plasma concentrations. Agents that might be coadministered with trimetrexate in AIDS patients for other indications that could elicit this activity include erythromycin, rifampin, rifabutin, ketoconazole, and fluconazole. *In vitro* perfusion of isolated rat liver has shown that cimetidine caused a significant reduction in trimetrexate metabolism and that acetaminophen altered the relative concentration of trimetrexate metabolites possibly by competing for sulfate metabolites. Based on an *in vitro* rat liver model, nitrogen substituted imidazole drugs (clotrimazole, ketoconazole, miconazole) were potent, non-competitive inhibitors of trimetrexate metabolism. Patients medicated with these drugs and trimetrexate should be carefully monitored.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Long term studies in animals to evaluate the carcinogenic potential of trimetrexate have not been performed.

Mutagenesis: Trimetrexate was not mutagenic when tested using the standard Ames *Salmonella* mutagenicity assay with and without metabolic activation. Trimetrexate did not induce mutations in Chinese hamster lung cells or sister-chromatid exchange in Chinese hamster ovary cells. Trimetrexate did induce an increase in the chromosomal aberration frequency of cultured Chinese hamster lung cells; however, trimetrexate showed no clastogenic activity in a mouse micronucleus assay.

Impairment of fertility: No studies have been conducted to evaluate the potential of trimetrexate to impair fertility. However, during standard toxicity studies conducted in mice and rats, degeneration of the testes and spermatocytes including the arrest of spermatogenesis was observed.

Pregnancy Category D

Pregnancy, teratogenic effects - See **WARNINGS**.

Nursing Mothers

It is not known if trimetrexate is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Neutrexin, it is recommended that breast feeding be discontinued if the mother is treated with Neutrexin.

Pediatric Use

The safety and effectiveness of Neutrexin for the treatment of histologically confirmed PCP has not been established for patients under 18 years of age. Under the Compassionate Use Protocol (maintained by U.S. Bioscience), 2 children, ages 15 months and 9 months, were treated with trimetrexate and leucovorin using a dose of 45 mg/m² of trimetrexate per day for 21 days and 20 mg/m² of leucovorin per day for 24 days. There were no serious or unexpected adverse effects.

ADVERSE REACTIONS

Because many patients who participated in clinical trials of Neutrexin (trimetrexate glucuronate for injection) had complications of advanced HIV disease, it is difficult to distinguish adverse events caused by Neutrexin from those resulting from underlying medical conditions.

Table 3 lists the adverse events that occurred in ≥ 1% of the patients who participated in the Comparative Study of Neutrexin plus leucovorin versus TMP/SMX.

TABLE 3
NEUTREXIN COMPARATIVE TRIAL
Comparison of Adverse Events Reported for ≥ 1% of Patients

Adverse Events	Number and Percent (%) of Patients with Adverse Events			
	TMTX/LV (n = 109)		TMP/SMX (n = 111)	
Non-Laboratory Adverse Events:				
Fever	9	(8.3)	14	(12.6)
Rash/Pruritus	6	(5.5)	14	(12.6)
Nausea/Vomiting	5	(4.6)[a]	15	(13.5)[a]
Confusion	3	(2.8)	3	(2.7)
Fatigue	2	(1.8)	0	(0.0)
Hematologic Toxicity:				
Neutropenia (≤ 1000/mm³)	33	(30.3)	37	(33.3)
Thrombocytopenia (≤ 75,000/mm³)	11	(10.1)	17	(15.3)
Anemia (Hgb < 8 g/dL)	8	(7.3)	10	(9.0)
Hepatotoxicity:				
Increased AST (>5 x ULN[b])	15	(13.8)	10	(9.0)
Increased ALT (>5 x ULN)	12	(11.0)	13	(11.7)
Increased Alkaline Phosphatase (>5 x ULN)	5	(4.6)	3	(2.7)
Increased Bilirubin (2.5 x ULN)	2	(1.8)	1	(0.9)
Renal:				
Increased Serum Creatinine (>3 x ULN)	1	(0.9)	2	(1.8)
Electrolyte Imbalance:				
Hyponatremia	5	(4.6)	10	(9.0)
Hypocalcemia	2	(1.8)	0	(0.0)
No. of Patients With at Least one Adverse Event[c]	58	(53.2)	60	(54.1)

[a] Statistically significant difference between treatment groups (Chi-square: p=0.022)

[b] ULN = Upper limit of normal range

[c] Patients could have reported more than one adverse event; therefore, the sum of adverse events exceeds the number of patients'

Laboratory toxicities were generally manageable with dose modification of trimetrexate/leucovorin (See **DOSAGE AND ADMINISTRATION**).

Table 4 lists the adverse events resulting in discontinuation of study therapy in the Neutrexin Comparative Study with TMP/SMX. Twenty-nine percent of the patients on the TMP/SMX arm discontinued therapy due to adverse events compared to 10% of the patients treated with TMTX/LV (p<0.001).

TABLE 4
NEUTREXIN COMPARATIVE TRIAL
Adverse Events Resulting in Discontinuation of Therapy

Adverse Events	Number and Percent (%) of Patients Discontinued for Adverse Events[a]			
	TMTX/LV (n = 109)		TMP/SMX (n = 111)	
Non-Laboratory Adverse Events:				
Rash/Pruritus	3	(2.8)	5	(4.5)
Fever	2	(1.8)	4	(3.6)
Nausea/Vomiting	1	(0.9)	8	(7.2)
Neurologic Toxicity	1	(0.9)[c]	2	(1.8)
Hematologic Toxicity:				
Neutropenia (≤ 1000/mm³)	4	(3.7)	6	(5.4)
Thrombocytopenia (≤ 75,000/mm³)	0	(0.0)	4	(3.6)
Anemia (Hgb < 8 g/dL)	0	(0.0)	4	(3.6)
Hepatotoxicity:				
Increased AST (>5 x ULN[a])	3	(2.8)	9	(8.1)
Increased ALT (>5 x ULN)	1	(0.9)	4	(3.6)
Increased Alkaline Phosphatase (>5 x ULN)	0	(0.0)	1	(0.9)
Electrolyte Imbalance:				
Hyponatremia	0	(0.0)	3	(2.7)
No. of Patients Discontinuing Therapy Due to an Adverse Event[b]	11	(10.1)[d]	32	(28.8)[d]

[a] ULN = Upper limit of normal range

[b] Patients could discontinue therapy due to more than one toxicity; therefore the sum exceeds number of patients who discontinued due to toxicity

[c] Patient discontinued TMTX/LV due to seizure, though causal relationship could not be established

[d] Statistically significant difference between treatment groups (Chi-square: p < 0.001)

Hematologic toxicity was the principal dose-limiting side effect. An anaphylactoid reaction has been reported in a cancer patient receiving Neutrexin as a bolus injection.

OVERDOSAGE

Neutrexin (trimetrexate glucuronate for injection) administered without concurrent leucovorin can cause lethal complications. There has been no extensive experience in humans receiving single intravenous doses of trimetrexate greater than 90 mg/m²/day with concurrent leucovorin. The toxicities seen at this dose were primarily hematologic. In the event of overdose, Neutrexin should be stopped and leucovorin should be administered at a dose of 40 mg/m² every 6 hours for 3 days. The LD_{50} of intravenous trimetrexate in mice is 62 mg/kg (186 mg/m²).

DOSAGE AND ADMINISTRATION

Caution: Neutrexin (trimetrexate glucuronate for injection) must be administered with concurrent leucovorin (leucovorin protection) to avoid potentially serious or life-threatening toxicities. Leucovorin therapy must extend for 72 hours past the last dose of Neutrexin.

Neutrexin (trimetrexate glucuronate for injection) is administered at a dose of 45 mg/m² once daily by intravenous infusion over 60-90 minutes. Leucovorin must be administered daily during treatment with Neutrexin and for 72 hours past the last dose of Neutrexin. Leucovorin may be administered intravenously at a dose of 20 mg/m² over 5 to 10 minutes every 6 hours for a total daily dose of 80 mg/m², or orally as 4 doses of 20 mg/m² spaced equally throughout the day. The oral dose should be rounded up to the next higher 25 mg increment. The recommended course of therapy is 21 days of Neutrexin and 24 days of leucovorin.

Dosage Modifications

Hematologic toxicity: Neutrexin (trimetrexate glucuronate for injection) and leucovorin doses should be modified based on the worst hematologic toxicity according to the following table. If leucovorin is given orally, doses should be rounded up to the next higher 25 mg increment.

TABLE 5
DOSE MODIFICATIONS FOR HEMATOLOGIC TOXICITY

			Recommended Dosages of	
Toxicity Grade	Neutrophils (Polys and Bands)	Platelets	Neutrexin	Leucovorin
1	> 1000/mm³	> 75,000/mm³	45 mg/m² once daily	20 mg/m² every 6 hours
2	750-1000/mm³	50,000-75,000/mm³	45 mg/m² once daily	40 mg/m² every 6 hours
3	500-749/mm³	25,000-49,999/mm³	22 mg/m² once daily	40 mg/m² every 6 hours
4	< 500/mm³	< 25,000/mm³	Day 1-9 Discontinue Day 10-21Interrupt up to 96 hrs[a]	40 mg/m² every 6 hours

[a] If Grade 4 hematologic toxicity occurs prior to Day 10, Neutrexin should be discontinued. Leucovorin (40 mg/m², q6h) should be administered for an additional 72 hours. If Grade 4 hematologic toxicity occurs at Day 10 or later, Neutrexin may be held up to 96 hours to allow counts to recover. If counts recover to Grade 3 within 96 hours, Neutrexin should be administered at a dose of 22 mg/m² and leucovorin maintained at 40 mg/m², q6h. When counts recover to Grade 2 toxicity, Neutrexin dose may be increased to 45 mg/m², but the leucovorin dose should be maintained at 40 mg/m² for the duration of treatment. If counts do not improve to ≤ Grade 3 toxicity within 96 hours, Neutrexin should be discontinued. Leucovorin at a dose of 40 mg/m², q6h should be administered for 72 hours following the last dose of Neutrexin.

Hepatic toxicity: Transient elevations of transaminases and alkaline phosphatase have been observed in patients treated with Neutrexin. Interruption of treatment is advisable if transaminase levels or alkaline phosphatase levels increase to >5 times the upper limit of normal range.

Renal toxicity: Interruption of Neutrexin is advisable if serum creatinine levels increase to > 2.5 mg/dL and the elevation is considered to be secondary to Neutrexin.

Other toxicities: Interruption of treatment is advisable in patients who experience severe mucosal toxicity that interferes with oral intake. Treatment should be discontinued for fever (oral temperature ≥ 105°F/40.5°C) that cannot be controlled with antipyretics.

Leucovorin therapy must extend for 72 hours past the last dose of Neutrexin.

RECONSTITUTION AND DILUTION

Neutrexin (trimetrexate glucuronate for injection) should be reconstituted with 2 mL of 5% Dextrose Injection, USP or Sterile Water for Injection, USP, to yield a concentration of 12.5 mg of trimetrexate per mL (complete dissolution should occur within 30 seconds). The reconstituted product will appear as a pale greenish-yellow solution and must be inspected visually for particulate matter prior to dilution. Do not use if cloudiness or precipitate is observed. This solution should be filtered (0.22µm) prior to dilution. Neutrexin should not be reconstituted with solutions containing either chloride ion or leucovorin, since precipitation occurs instantly.

After reconstitution, the solution is stable under refrigeration or at room temperature for up to 24 hours. Do not freeze reconstituted solution. Discard the unused portions after 24 hours.

Reconstituted solution should be further diluted with 5% Dextrose Injection, USP, to yield a final concentration of 0.25 to 2 mg of trimetrexate per mL. The diluted solution should be administered by intravenous infusion over 60 minutes. Neutrexin should not be mixed with solutions containing either chloride ion or leucovorin, since precipitation occurs instantly. It is stable under refrigeration or at room temperature for up to 24 hours. Do not freeze. Discard the unused portions after 24 hours after initial reconstitution. The intravenous line must be flushed thoroughly with at least 10 mL of 5% Dextrose Injection, USP, before and after administering Neutrexin.

Leucovorin protection may be administered prior to or following Neutrexin. In either case the intravenous line must be flushed thoroughly with at least 10 mL of 5% Dextrose Injection, USP. Leucovorin Calcium for injection should be diluted according to the instructions in the leucovorin package insert, and administered over 5 to 10 minutes every 6 hours.

Caution: Parenteral products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Neutrexin forms a precipitate instantly upon contact with chloride ion or leucovorin, therefore it should not be added to solutions containing sodium chloride or other anions. Neutrexin and leucovorin solutions must be administered separately. Intravenous lines should be flushed with at least 10 mL of 5% Dextrose Injection, USP, between Neutrexin and leucovorin infusions.

HANDLING AND DISPOSAL

If Neutrexin (trimetrexate glucuronate for injection) contacts the skin or mucosa, immediately wash thoroughly with soap and water. Procedures for proper disposal of cytotoxic drugs should be considered. Several guidelines on this subject have been published (1-5).

HOW SUPPLIED

Neutrexin (trimetrexate glucuronate for injection) (NDC 58178-020-01) is supplied as a sterile lyophilized powder in 5 mL, single-dose vials. Each 5 mL vial contains trimetrexate glucuronate equivalent to 25 mg of trimetrexate. The vials are packaged and available in four market presentations as listed below:

Bulk Pack - 4 trays of 25 vials per shrink-wrapped tray (NDC 58178-020-70)
10 Pack - 10 vials in a white chip-board carton (NDC 58178-020-10)
50 Pack - 2 trays of 25 vials per shrink-wrapped tray (NDC 58178-020-50)
Starter Pack - 21 vials per shrink-wrapped tray (NDC 58178-020-21) presented in combination with 28 vials of Leucovorin Calcium for Injection in a shrink-wrapped tray. Each vial contains 50 mg of leucovorin as the calcium salt.

Store at controlled room temperature 15° to 30°C (59° to 86°F). **Protect from exposure to light.**

REFERENCES

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2. Clinical Oncological Society of Australia: Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. *Medical Journal of Australia* 1: 426-428, 1983.
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4. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic Drugs in Hospitals. *American Journal of Hospital Pharmacy* 42: 131-137, 1985.
5. OSHA Work Practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic) Drugs. *American Journal of Hospital Pharmacy* 43: 1193-1204, 1986.

Manufactured by:
Ben Venue Laboratories, Inc.
Bedford, Ohio 44146

Revision Date 12/93

For:
BIOSCIENCE
West Conshohocken, PA 19428

Exhibit 2

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 17 1993

NDA 20-326

U.S. Bioscience
Attention: Ms. Carol S. Marchione
Director, Regulatory Affairs
P.O. Box 851
West Conshohocken, PA 19428

Dear Ms. Marchione:

Reference is made to your New Drug Application dated February 1, 1993, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Neutrexin™ (trimetrexate glucuronate for injection).

This NDA provides for the use of Neutrexin™ with concurrent leucovorin administration (leucovorin protection) as an alternative therapy for the treatment of moderate-to-severe Pneumocystis carinii pneumonia (PCP) in immunocompromised patients, including patients with acquired immunodeficiency syndrome (AIDS), who are intolerant of, or are refractory to, trimethoprim-sulfamethoxazole therapy or for whom trimethoprim-sulfamethoxazole is contraindicated.

We have completed the review of this application, as amended, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling dated December 3, 1993, and the draft carton and

container labels dated November 30, 1993, with the minor modifications you agreed to during your December 3, 1993, telephone conversation with Mr. David Isom of this agency. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the referenced draft labeling. Marketing the product before making, exactly as agreed to, the revisions in the product's labeling may render the product misbranded and an unapproved drug.

Please submit 12 copies of the FPL as soon as it is available. Please individually mount seven of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated as "Final Printed Labeling for approved NDA 20-326." Approval of this labeling by FDA is not required before the labeling is used.

Please submit one market package of the drug product when it is available.

[redacted]

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81. [redacted]

If you have any questions, please contact Mr. David Isom at 301-443-9553.

Sincerely yours,

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation
and Research

Enclosure

Exhibit 3

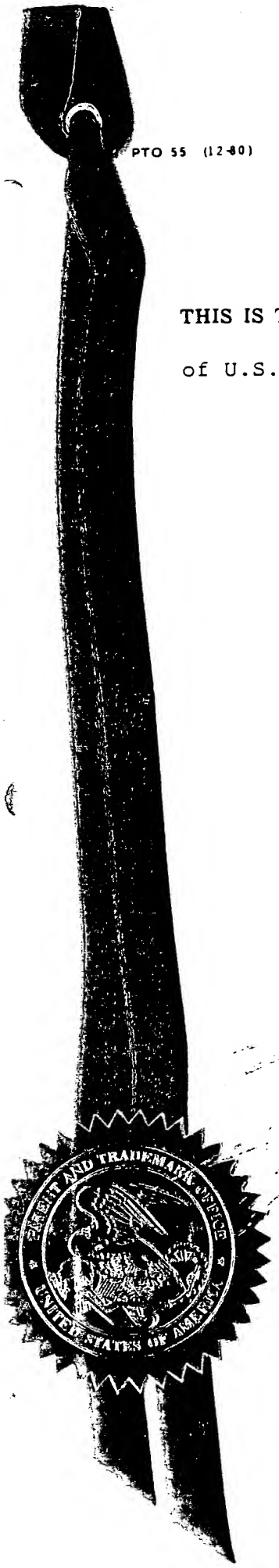
PTO 55 (12-80)

U. S. DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

January 24, 1994
(Date)

THIS IS TO CERTIFY that the annexed is a true copy from the records of this office

of U.S. Patent 4,376,858.



By authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

P. Sullivan

Certifying Officer.

United States Patent [19]

Colbry

[11] **4,376,858**

[45] **Mar. 15, 1983**

[54] **2-4-DIAMINO-5-METHYL-6-[(3,4,5-TRIMETHOXYANILINO)METHYL]QUINAZOLINE SALTS**

[75] Inventor: **Norman L. Colbry**, Gregory, Mich.

[73] Assignee: **Warner Lambert Company**, Morris Plains, N.J.

[21] Appl. No.: **344,350**

[22] Filed: **Jan. 29, 1982**

Related U.S. Application Data

[63] Continuation of Ser. No. 202,512, Oct. 31, 1980, abandoned.

[51] **Int. Cl.**[3] **C07D 239/84**; A61K 31/505

[52] **U.S. Cl.** **544/291**; 424/251

[58] **Field of Search** 544/291; 424/251

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,471,498	10/1969	Davoll	544/291
3,485,842	12/1969	Davoll	544/291
3,560,502	2/1971	Davoll	544/291

FOREIGN PATENT DOCUMENTS

1104576	2/1968	United Kingdom	544/291
1345502	1/1974	United Kingdom	544/291

OTHER PUBLICATIONS

McElvain, *The Characterization of Organic Compounds*, Revised Edition, 1953, The Macmillian Co., pp. 44–47; 72–75.

Berge, et al., "J. Pharm. Sci.," vol. 66, No. 1, 1977, pp. 1–19.

Primary Examiner—Donald G. Daus
Assistant Examiner—James H. Turnipseed
Attorney, Agent, or Firm—Ronald A. Daignault

[57] **ABSTRACT**

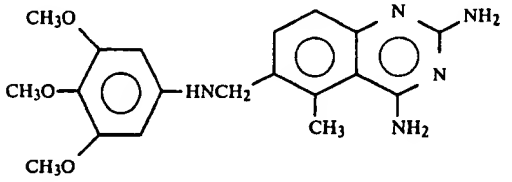
2,4-Diamino-5-methyl-6-[(3,4,5-trimethoxyanilino)methyl]quinazoline salts, pharmaceutical compositions containing said salts, methods of treating malaria, and bacterial infections employing said salts and compositions and methods for producing said salts.

5 Claims, No Drawings

2-4-DIAMINO-5-METHYL-6-[(3,4,5-TRIMETHOXYANILINO)METHYL]QUINAZOLINE SALTS

This is a continuation of application Ser. No. 202,512, filed Oct. 31, 1980 and now abandoned.

The compound 2,4-diamino-5-methyl-6-[(3,4,5-trimethoxyanilino)methyl]quinazoline is reported in Great Britain Patent Specification No. 1,345,502, which is incorporated by reference, as exhibiting antimalarial and antibacterial activity. This compound, which has the formula

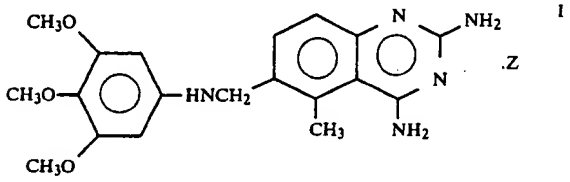


has also been reported to exhibit antineoplastic activity in Biochemical Pharmacology 28, 1983–1987(1978) and Cancer Research 39, 293–304(1979). Unfortunately, the salts that have been studied to date do not have a high degree of water solubility. This is especially deleterious when treating neoplasms since injectable routes are preferred.

Salts can be found to be unacceptable for a host of reasons: Lack of solubility, high toxicity, unstability, non-crystalline structure, not recognized as safe by the United States Food and Drug Administration, etc.

The present invention relates to soluble, nontoxic, stable, crystalline salts having the names 2,4-diamino-5-methyl-6-[(3,4,5-trimethoxyanilino)methyl]quinazoline monoisethionate and 2,4-diamino-5-methyl-6-[(3,4,5-trimethoxyanilino)methyl]quinazoline glucuronate.

The salts of the invention are shown by the following formula



I

wherein Z is 2-hydroxyethanesulfonic acid or glucuronic acid. The term glucuronic acid is intended to encompass all the isomeric forms of glucuronic acid with the preferred form being the naturally occurring form of glucuronic acid.

The compounds of formula I wherein Z is 2-hydroxyethanesulfonic acid or glucuronic acid are prepared by reacting 2,4-diamino-5-methyl-6-[(3,4,5-trimethoxyanilino)methyl]quinazoline with 2-hydroxyethanesulfonic acid or glucuronic acid, respectively.

The ratio of reactants is not critical and while equimolar quantities of reactants may be employed an excess of acid is generally preferred.

The reaction is carried out in a polar solvent, such as methanol, ethanol, acetone, water, etc., or mixtures thereof. The reaction may be carried out at temperatures from about 0° C. to about 100° C. (depending on the boiling point of the solvents used) for periods of from about a few minutes to about twenty-four hours. A more preferred range of conditions is about 25° C. to about 80° C. for about one to eight hours.

It should be noted that the reaction can take place using a suspension of the base in the polar solvent.

The two compounds of the invention exhibit excellent properties for use as pharmaceuticals. The 2,4-diamino-5-methyl-6-[(3,4,5-trimethoxyanilino)methyl]-quinazoline monoisethionate salt is a stable, crystalline, highly water soluble salt. The 2,4-diamino-5-methyl-6-[(3,4,5-trimethoxyanilino)methyl]quinazoline glucuronate salt appears to be powdery rather than crystalline, but has a higher degree of solubility.

These conclusions are based on the results of experiments reported in Tables I and II. Table I reports the results of experiments where 2,4-diamino-5-methyl-6-[(3,4,5-trimethoxyanilino)methyl]quinazoline is added to an aqueous acidic solution, while Table II reports the solubility of prepared 2,4-diamino-5-methyl-6-[(3,4,5-trimethoxyanilino)methyl]quinazoline salts. A comparison of the results obtained from the two methods is reported in Table III.

Most salts were found to have an unsatisfactory degree of solubility in water, such as the 2-naphthalene sulfonate; undesirable amorphous form, such as the gluconate or galacturonate, or not acceptable because extensive studies to determine safety would have to be performed, such as ethoxyacetic acid.

The compounds of this invention are useful in treating malaria or as an antibacterial in mammals, such as dogs, cats, cattle, etc., in dosage unit form with the dose adjusted to the needs and tolerances of the subject being treated. The usual mammalian dosage range for a 70 kg subject is from about 3.5 to 350 mg per day (0.05 mg to 5.0 mg per kg of body weight per day), preferably 7.0 mg to 140 mg per day (0.1 mg to 2.0 mg per kg of body weight per day).

TABLE I

2,4-Diamino-5-methyl-6-[3,4,5-trimethoxyanilino)-methyl]quinazoline Solubility in Aqueous Acids

Acid	ph. 1 M soln.	Base Solubility in acid soln.
Glucuronic	2.05	34.35 mg base/ml
Gluconic	2.27*	19.8
Ethoxyacetic	2.20	19.5
Galacturonic	2.28	25.1
Ethoxyacetic	2.35*	19.7
Isethionic	1.20	16.3
Isethionic	1.46*	17.3
N—(Morpholine)ethane-2-sulfonic	1.52	11.2
Methane sulfonic	1.00	9.83
Methane sulfonic	1.42*	6.49
Citric	1.95	8.28
Benzene sulfonic	0.95	7.17
Benzene sulfonic	1.48*	1.89
Glycolic	3.00	4.13
Glycolic	3.28*	4.73
p-Toluene sulfonic	1.45	2.74
d-Tartaric	1.82	1.57
(2-Pyridyl)-2-ethane sulfonic	3.35	1.73
2-Amino-ethane sulfonic	4.28	.51
2-Naphthalene sulfonic	1.05	.15 max.

*ph of .05 M acid - test method using 1/1 acid/base

Method: 0.1 M acid solutions, 10.0 ml, prepared—185±3 mg of 2,4-diamino-5-methyl-6-[(3,4,5-trimethoxyanilino)methyl]quinazoline added (0.05 M in base)—the mixture shaken 4–12 hours, filtered, and 1.0 ml of filtrate diluted with 0.01 NHCl to read UV absorbance at 321 nm.

TABLE II

Solubility of 2,4-Diamino-5-methyl-6-[(3,4,5-trimethoxyanilino)methyl]quinazoline Salts in Water

Salt	Method	Solubility mg base/ml
Glucuronate	B	109.4
Isethionate	B	24.78
Isethionate	A	23.93
Ethoxyacetate	B	6.3
3-Hydroxypropyl sulfonate	B	4.73
Lactate	A	4.34
Hydrochloride	A	3.22
Gluconatete	B	2.55
Ethane sulfonate	B	2.64
Acetate	A	1.72
Sulfate	A	1.61
Gentisate	A	1.4–7.06*
Gentisate	B	0.28
Benzene sulfonate	B	1.24
Free base - 2,4-diamino-5-methyl-6-[(3,4,5-trimethoxy-anilino)methyl]-quinazoline	A	0.2
Free base - 2,4-diamino-5-methyl-6-[(3,4,5-trimethoxy-anilino)methyl]-quinazoline	B	0.1

*Analytical sample preparation questionable.

Method A: Saturated 2.0 ml H_2O overnight, 0.5 ml of filtrate diluted to 10.0 ml with methanol, added 1 drop of 6 N KOH to UV cell.

Method B: Saturated 5.0 ml H_2O overnight, 1.0 ml of filtrate diluted with 0.01 N HCl (10 to 250 fold dilutions).

TABLE III

Method Comparison - 2,4-Diamino-5-methyl-6-[(3,4,5-trimethoxyanilino)methyl]quinazoline Salts

	Acid		Acid/	Solubility	Filtrate
	Conc. (M)	pH	Base	mg base/ml	pH
Isethionic	.1	1.20	2/1	16.33*	1.83
	.05	1.46	1/1	17.34*	3.70
	Prepared Salt			24.8	5.30
Ethoxyacetic	.1	2.20	2/1	19.5*	
	.065	2.35	1/1	19.7*	4.15
	Prepared Salt			6.3	5.32
Methane	.1	1.00	1/.9	8.74	
	.06	1.42	1/1	6.5	3.00
	Prepared Salt			4.9	5.32
Benzene	.1	0.95	2/1	7.17	2.95
sulfonic	.05	1.48	1/1	1.89	2.95
	Prepared Salt			1.24	4.45
Glycolic	.1	2.68	2/1	4.13	3.00
	.1	2.69	1/1	4.73	3.28
	Prepared Salt			2.55	5.30

*Not saturated, base solubility equals amount of base available in shake out preparation.

The compounds of this invention may be administered orally, parenterally or rectally.

In accordance with the invention, oral pharmaceutical compositions are produced by formulating the compounds of the invention, as the active ingredient, in dosage unit forms with a pharmaceutical carrier. Some examples of dosage unit forms are tablets, capsules, lozenges, and pills; as well as powders and aqueous and non-aqueous solutions and suspensions packaged in containers containing either one or some larger number of dosage units and capable of being sub-divided into individual doses by such means as measurement into a teaspoon or other standard container. Some examples of suitable pharmaceutical carriers, including pharmaceutical diluents, are gelatin capsules; sugars such as lactose and sucrose; starches such as corn starch and potatoe starch; cellulose derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, methyl cellulose, and cellulose acetate phthalate; gelatin; talc; stearic acid; magnesium stearate; vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil, and oil of theobroma; propylene glycol; glycerine, sorbitol; polyethylene glycol; water; agar; alginic acid; as well as other compatible substances normally used in pharmaceutical formulations. The compositions of the invention can also contain other components such as coloring agents, flavoring agents, and/or preservatives. These materials, if present, are usually used in relatively small amounts. The compositions can, if desired, also contain other therapeutic agents.

The compounds of the invention when intended for parenteral use could be dissolved in an isotonic aqueous solution containing other materials such as buffers, preservatives, etc. It may also be placed in the form of an sterile lyophilized material to be taken up in an appropriate vehicle at time of use.

Lastly, the compounds of the invention may be administered in the form of a suppository using glycerin, cocoa butter, etc., as a vehicle. The vehicle may also contain preservatives and coloring agents.

The percentage of the active ingredient in the foregoing compositions can be varied within wide limits but for practical purposes it is preferably present in a concentration of at least 10% in a solid composition and at least 2% in a primarily liquid composition. The most satisfactory compositions are those in which a much higher proportion of the active ingredient is present. The compositions of the invention preferably contain from 1 to 100 mg, preferably 2 to 50 mg of the active ingredient per dosage unit so that the entire amount to be administered during a day can be made up from a reasonable number of dosage units.

The compounds can be combined with other antimalarial compounds, such as quinine, chloroquine, etc., and used in the above described manner.

The compounds of the invention inhibit the growth of pathogenic bacteria, such as *Streptococcus faecalis* (MGH-2), normal (UC-76) and drug-resistant (S18713) *Staphyloccus aureus; Escherichia coli* (Vogel) and *Shigella sonnei* (C-10). Thus, the compounds would be useful in the sterilization of laboratory glassware, etc.

STARTING MATERIALS

2-Hydroxyethanesulfonic acid solution

A solution of 10 g of 2-hydroxyethane sulfonic acid, sodium salt in 30 ml of H_2O is eluted through 120 g of an acid form ion exchange column [Dowex 50WX8 (Dow Chemical Co., Midland, Mich.)]. The resulting acidic solution (200 ml) is titrated and found to be 0.304 molar in the desired acid.

EXAMPLE 1

2,4-Diamino-5-methyl-6-[(3,4,5-trimethoxyanilino)methyl]quinazoline monoisethionate

A slurry of 2,4-diamino-5-methyl-6-[(3,4,5-trimethoxyanilino)methyl]quinazoline monoacetate (59.2 g) Great Britain Patent Specification No. 1,345,502 in water (1.5.1) at 80° C. is treated with acetic acid (200 ml). The resulting solution is made basic (pH 10) by addition of 50% NaOH. The slurry is cooled by addi-

tion of ice and the solid collected. Drying (100° C., 1 torr, 2 hours) gives the free base as a light green-yellow powder.

A slurry of the free base (22.9 g) in acetone (1 l) is treated with 0.304 M aqueous 2-hydroxyethanesulfonic acid (204 ml) cooled and filtered to remove a small amount of solid. The filtrate is concentrated to a solid which is recrystallized from a mixture of ethanol (400 ml) and acetone (400 ml) and dried (80° C., 1 torr, 4 hours) to give the title compound, mp 189°-191° C.

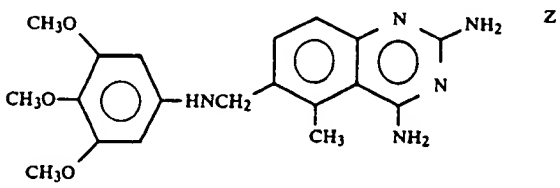
EXAMPLE 2

2,4-Diamino-5-methyl-6-[(3,4,5-trimethoxyanilino)methyl]quinazoline D-glucuronate

A mixture of 2,4-diamino-5-methyl-6-[(3,4,5-trimethoxyanilino)methyl]quinazoline (1.0 g) and glucuronic acid (0.7 g) in methanol (65 ml) is heated to dissolve the solid. The solution is cooled to 10° C. and filtered to remove a small amount of solid. The filtrate is heated to reflux and ethyl acetate is added to the cloud point. The warm solution is filtered then slowly cooled. The solid that forms is collected, washed first with ethylacetate, then with ether and dried in vacuo at 60° C. to give the salt as a yellow powder with no definite melting point.

I claim:

1. A compound of the formula



wherein Z is 2-hydroxyethanesulfonic acid or glucuronic acid.

2. The compound of claim 1 having the name 2,4-diamino-5-methyl-6-[(3,4,5-trimethoxyanilino)methyl]-quinazoline monoisethionate.

3. The compound of claim 1 having the name 2,4-diamino-5-methyl-6-[(3,4,5-trimethoxyanilino)methyl]-quinazoline glucuronate.

4. The compound of claim 2 being in crystalline form.

5. The compound of claim 3 being in powdery form.

* * * * *

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Exhibit 4

1/

RONALD A. DAIGNAULT
WARNER-LAMBERT COMPANY
2800 PLYMOUTH ROAD
ANN ARBOR, MICHIGAN 48105

DATE MAILED
06/25/86

006339

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

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If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STA
1	[redacted]	170	225		[redacted]	03/15/83	01/29/82	04	NO	PAI

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PART A

MA ER DATA CENTER, INC.
29100 NORTHWESTERN HWY. SUITE 300
SOUTHFIELD, MICHIGAN 48034-1095
U.S.A.

06/06/86

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WASHINGTON, D.C. 20231

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PLEASE APPLY THE REMITTANCE ENCLOSED TO PAY THE ANNUITIES ON THE FOLLOWING APPLICATIONS AND PATENTS WHICH BECOME DUE DURING THE PERIOD FROM JULY 1986 THROUGH SEPTEMBER 1986.

1. PATENT NUMBER	2. FEE CODE	3. MAINTENANCE FEE AMT	4. SRCHRG AMOUNT	5. U.S. SERIAL NUMBER	6. PAT DATE MM/DD/YY	7. APP DATE MM/DD/YY	8. PAY YEAR	9. SM EN
4376858	170	225.		344350	03/15/83	01/29/82	04	

TOTAL PAYMENT 225.00

A CHECK INCLUDING THE AMOUNT WHICH IS DUE FOR THE ABOVE ANNUITIES IS ENCLOSED.

WARNER-LAMBERT COMPANY AKA
WARNER-LAMBERT PHARMACEUTICALS
C/O MASTER DATA CENTER, INC
24700 NORTHWESTERN HWY. SUITE 300
SOUTHFIELD, MICHIGAN 48075 U.S.A.

MASTER DATA CENTER INC.

PAYOR NUMBER: 000124

(313)352-5810

060 06/23/86 4376858 2 170 225.00 CK

PD-2798

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RONALD A. DAIGNAULT
WARNER-LAMBERT COMPANY
2800 PLYMOUTH ROAD
ANN ARBOR, MICHIGAN 48105

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ITM NBR	PATENT NUMBER	FEE CODE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,376,858	171	495	----	06/344,350	03/15/83	01/29/82	08	NO	PAID

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WHICH BECOME DUE DURING THE PERIOD FROM SEPTEMBER 1990

1. PATENT NUMBER	2. FEE CODE	3. MAINTENANCE FEE AMT	4. SRCHRG AMOUNT	5. U.S. SERIAL NUMBER	6. PAT DATE MM/DD/YY	7. APP DATE MM/DD/YY	8. PAY YEAR
4376858	171	495.		344350	03/15/83	01/29/82	08
4650805	173	490.		803697	03/17/87	12/02/85	04
4654372	173	490.		818505	03/31/87	01/10/86	04

TOTAL PAYMENT 1,475.00

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DUE FOR THE ABOVE ANNUITIES IS ENCLOSED.

WARNER-LAMBERT COMPANY AKA
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MASTER DATA CENTER INC.

PAYOR NUMBER: 000124

(313)352-5810

090 HB 09/07/90 4376858 2 171 495.00 CK

Ref. No. 1 Exhibit 5

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0014
Expiration Date: December 31, 1984

NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION FOR A NEW DRUG

NOTE: No drug may be shipped or study initiated unless a complete statement has been received. *(21 CFR 312.1(a)(2)).*

Name of Sponsor Warner-Lambert Company Date MAR 9 1987

Address 2800 Plymouth Road, P.O. Box 1047
Ann Arbor, Michigan 48106 Telephone (313) 996-7428

Name of Investigational Drug Trimetrexate Glucuronate Parenteral

FOR A DRUG:

Food And Drug Administration
Office of New Drug Evaluation *(HFN-106)*
5600 Fishers Lane
Rockville, Maryland 20857

FOR A BIOLOGIC:

Food and Drug Administration
Office of Biologics *(HFN-823)*
8800 Rockville Pike
Bethesda, Maryland 20205

Dear Sir:

The sponsor, Warner-Lambert Company, submits this notice of claimed investigational exemption for a new drug under the provisions of section 505(i) of the Federal Food, Drug, and Cosmetic Act and § 312.1 of Title 21 of the Code of Federal Regulations.

Attached hereto in triplicate are:

1. The best available descriptive name of the drug, including to the extent known the chemical name and structure of any new-drug substance, and a statement of how it is to be administered. (If the drug has only a code name, enough information should be supplied to identify the drug.)

2. Complete list of components of the drug, including any reasonable alternates for inactive components.

3. Complete statement of quantitative composition of drug, including reasonable variations that may be expected during the investigational stage.

4. Description of source and preparation of, any new-drug substances used as components, including the name and address of each supplier or processor, other than the sponsor, or each new-drug substance.

5. A statement of the methods, facilities, and controls used for the manufacturing, processing, and packing of the new drug to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for safety and to give significance to clinical investigations made with the drug.

6. A statement covering all information available to the sponsor derived from preclinical investigations and any clinical studies and experience with the drug as follows:

a. Adequate information about the preclinical investigations, including studies made on laboratory animals, on the basis of which the sponsor has concluded that it is reasonably safe to initiate clinical investigations with the drug: Such information should include identification of the person who conducted each investigation; identification and qualifications of the individuals who evaluated the results and concluded that it is reasonably safe to initiate clinical investigations with the drug and a statement of where the investigations were conducted and where the records are available for inspection; and enough details about the investigations to permit scientific review. The preclinical investigations shall not be considered adequate to justify clinical testing unless they give proper attention to the conditions of the proposed clinical testing. When this information, the outline of the plan of clinical pharmacology, or any progress report on the clinical pharmacology, indicates a need for full review of the preclinical data before a clinical trial is undertaken, the Department will notify the sponsor to submit the complete preclinical data and to withhold clinical trials until the review is completed and the sponsor notified. The Food and Drug Administration will be prepared to confer with the sponsor concerning this action.

b. If the drug has been marketed commercially or investigated (e.g. outside the United States), complete information about such distribution or investigation shall be submitted, along with a complete bibliography of any publications about the drug.

c. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of preexisting information from preclinical and clinical investigations and experience with its components, including all reports available to the sponsor suggesting side-effects, contraindications, and ineffectiveness in use of such components: Such summary should include an adequate bibliography of publications about the components and may incorporate by reference any information concerning such components previously submitted by the sponsor to the Food and Drug Administration. Include a statement of the expected pharmacological effects of the combination.

d. If the drug is a radioactive drug, sufficient data must be available from animal studies or previous human studies to allow a reasonable calculation of radiation absorbed dose upon administration to a human being.

7. A total (one in each of the three copies of the notice) of all informational material, including label and labeling, which is to be supplied to each investigator: This shall include an accurate description of the prior investigations and experience and their results pertinent to the safety and possible usefulness of the drug under the conditions of the investigation. It shall not represent that the safety or usefulness of the drug has been established for the purposes to be investigated. It shall describe all relevant hazards, contraindications, side-effects, and precautions suggested by prior investigations and experience with the drug under investigation and related drugs for the information of clinical investigators.

8. The scientific training and experience considered appropriate by the sponsor to qualify the investigators as suitable experts to investigate the safety of the drug, bearing in mind what is known about the pharmacological action of the drug and the phase of the investigational program that is to be undertaken.

9. The names and a summary of the training and experience of each investigator and of the individual charged with monitoring the progress of the investigation and evaluating the evidence of safety and effectiveness of the drug as it is received from the investigators, together with a statement that the sponsor has obtained from each investigator a completed and signed form, as provided in subparagraph (12) or (13) of this paragraph, and that the investigator is qualified by scientific training and experience as an appropriate expert to under-

take the phase of the investigation outlined in section 10 of the "Notice of Claimed Investigational Exemption for a New Drug." (In crucial situations, phase 3 investigators may be added and this form supplemented by rapid communication methods, and the signed Form FD-1573 shall be obtained promptly thereafter.)

10. An outline of any phase or phases of the planned investigations and a description of the institutional review committee, as follows:

a. Clinical pharmacology. This is ordinarily divided into two phases: Phase I starts when the new drug is first introduced into man - only animal and in vitro data are available - with the purpose of determining human toxicity, metabolism, absorption, elimination, and other pharmacological action, preferred route of administration, and safe dosage range; phase 2 covers the initial trials on a limited number of patients for specific disease control or prophylaxis purposes. A general outline of these phases shall be submitted, identifying the investigator or investigators, the hospitals or research facilities where the clinical pharmacology will be undertaken, any expert committees or panels to be utilized, the maximum number of subjects to be involved, and the estimated duration of these early phases of investigation. Modification of the experimental design on the basis of experience gained need be reported only in the progress reports on these early phases, or in the development of the plan for the clinical trial, phase 3. The first two phases may overlap and, when indicated, may require additional animal data before these phases can be completed or phase can be undertaken. Such animal tests shall be designed to take into account the expected duration of administration of the drug to human beings, the age groups and physical status, as for example, infants, pregnant women, premenopausal women, of those human beings to whom the drug may be administered, unless this has already been done in the original animal studies. If a drug is a radioactive drug, the clinical pharmacology phase must include studies which will obtain sufficient data for dosimetry calculations. These studies should evaluate the excretion, whole body retention, and organ distribution of the radioactive material.

b. Clinical trial. This phase 3 provides the assessment of the drug's safety and effectiveness and optimum dosage schedules in the diagnosis. treatment, or prophylaxis of groups of subjects involving a given disease or condition. A reasonable protocol is developed on the basis of the facts accumulated in the earlier phases, including completed and submitted animal studies. This phase is conducted by separate groups following the same protocol (with reasonable variations and alternatives permitted by the plan) to produce well-controlled clinical data. For this phase, the following data shall be submitted:

i. The names and addresses of the investigators. (Additional investigators may be added.)

ii. The specific nature of the investigations to be conducted, together with information or case report forms to show the scope and detail of the planned clinical observations and the clinical laboratory tests to be made and reported.

iii. The approximate number of subjects (a reasonable range of subjects is permissible and additions may be made), and criteria proposed for subject selection by age, sex, and condition.

iv. The estimated duration of the clinical trial and the intervals, not exceeding 1 year, at which progress reports showing the results of the investigations will be submitted to the Food and Drug Administration.

c. Institutional review board (IRB). The sponsor must give assurance that an IRB that complies with the requirements set forth in Part 56 of this chapter will be responsible for the initial and continuing review and approval of the proposed clinical study. The sponsor must also provide assurance that the investigators will report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and that the investigators will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazard to the human subjects. FDA will regard the signing of the Form FDA-1571 as providing the necessary assurances above.

(The notice of claimed investigational exemption may be limited to any one or more phases, provided the outline of the additional phase or phases is submitted before such additional phases begin. A limitation on an exemption does not preclude continuing a subject on the drug from phase 2 to phase 3 without interruption while the plan for phase 3 is being developed.)

Ordinarily, a plan for clinical trial will not be regarded as reasonable unless, among other things, it provides for more than one independent competent investigator to maintain adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated, and comparable records on any individuals employed as controls. These records shall be individual records for each subject maintained to include adequate information pertaining to each, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, adequate information concerning any other treatment given and a full statement of any adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation.

11. A statement that the sponsor will notify the Food and Drug Administration if the investigation is discontinued, and the reason therefor.

12. A statement that the sponsor will notify each investigator if a new-drug application is approved, or if the investigation is discontinued.

13. If the drug is to be sold, a full explanation why sale is required and should not be regarded as the commercialization of a new drug for which an application is not approved.

14. A statement that the sponsor assures that clinical studies in humans will not be initiated prior to 30 days after the date of receipt of the notice by the Food and Drug Administration and that he will continue to withhold or to restrict clinical studies if requested to do so by the Food and Drug Administration prior to the expiration of such 30 days. If such request is made, the sponsor will be provided specific information as to the deficiencies and will be afforded a conference on request. The 30-day delay may be waived by the Food and Drug Administration upon a showing of good reason for such waiver; and for investigations subject to institutional review committee approval as described in item 10c above, and additional statement assuring that the investigation will not be initiated prior to approval of the study by such committee.

15. When requested by the agency, an environmental impact analysis report pursuant to § 25.1 of this chapter.

16. A statement that all nonclinical laboratory studies have been, or will be, conducted in compliance with the good laboratory practice regulations set forth in Part 58 of this chapter, or, if such studies have not been conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in conducting the study and those required in the regulations.

Very truly yours,

Original signed by

SPONSOR	PER T. N. T. Olson
Warner-Lambert Company	T. N. T. Olson, Ph.D.
	INDICATE AUTHORITY
	Director, Regulatory Liaison and Compliance

(This notice may be amended or supplemented from time to time on the basis of the experience gained with the new drug. Progress reports may be used to update the notice.)

ALL NOTICES AND CORRESPONDENCE SHOULD BE SUBMITTED IN TRIPLICATE.

IND FILE
COPY
Exhibit 6

WARNER LAMBERT

Memorandum

Memo to / Location: Trimetrexate (CI-898) IND 23,269 File
Ann Arbor

Date: September 2, 1987

From / Location: T. N. T. Olson
Ann Arbor

Subject: Phone Call From Mr. James D. Bona (301/443-6797) Regarding the Clinical Hold on the Clinical Study with Trimetrexate for Pneumocystis.

Mr. Bona in response to my phone call of September 1, 1987, phoned at 9:30 on September 2, 1987 to inform me that he had just spoken with Dr. Tabor and that the clinical hold had been lifted. He said that he was preparing a letter to us and that we should receive it within a week (or so).

I also informed him that NIAID would be submitting for their approval a Treatment IND within the next week. He said that Dr. Tabor had spoken with Dr. Bruce Chabner the previous day about that IND. Dr. Chabner had informed Dr. Tabor that IRBs were refusing to take part in the Treatment IND because of the clinical hold imposed on the large NIH clinical study. Mr. Bona indicated that with the clinical hold lifted NIAID would now be permitted to obtain approval of the Treatment IND.

I next raised the subject of the recently completed NIAID clinical studies being used as the second required clinical study for the NDA. I stated that just because it was a Phase 1 or 2 study did not preclud it from being a pivotal NDA study as insinuated by Dr. Albrecht. He agreed that under certain conditions that such a study could be utilized as the second study. I requested that if the results of the soon to be initiated NIH study were good, would he discuss the use of the completed study as one of the two studies with Dr. Tabor. He agreed to have this discussion with Dr. Tabor at an appropriate time and acknowledged that some kind of NDA approval would be politically necessary if the second NIH study results were profound.

Next I questioned him about the number of patients that would be necessary for proof of safety in such an NDA. I indicated that it looked like about 200 patients on trimetrexate would be available for such an NDA and would that be sufficient. I suggested that if it were not, then the patients being entered into the Treatment IND would become very important. I described to him the requirement of 1000 patients of the Cardio-Renal Division and the fact that we had a proposed NDA turned down because it only had 500 patients in it. He said that his Division did not have such a requirement, at least one that he was aware of, and that he would also discuss that with Dr. Tabor.

T. N. T. Olson

cc Dr. J. Bender
Dr. F. Kapp
Mr. C. Lents
Dr. D. Maxwell
Mr. J. Meisenhelder

REGULATORY LIAISON AND COMPLIANCE

October 13, 1987

To: Dr. J. F. Bender
Dr. H. L. Dickstein
Dr. J. F. Kapp
Mr. C. E. Lents
Dr. D. R. Maxwell
Dr. T. N. T. Olson

Re: FDA APPROVAL OF THE NIAID P. CARINII CLINICAL STUDY

Attached for your information and files is a letter from Dr. Edward Tabor of the FDA to Dr. Maureen W. Myers of NIAID dated October 7 approving the above clinical study. Mr. J. Bona, FDA CSO, sent us this information.

We expect written approval of our IND 29,796 for this same clinical study very soon. Verbal approval of our IND was received from Dr. Tabor via Mr. Bona to Dr. Olson on September 2.

J. E. Meisenhelder

JEM:LMD

Attachment 1

cc & att.: IND 29,796 (CI-898)
Regulatory Affairs, MP

Exhibit 7

US BIOSCIENCE

Barbara Scheffler

Senior Vice President
Clinical Operations and Regulatory Affairs

February 1, 1993

via Federal Express

David Feigal, M.D.
Division Director
Division of Anti-Viral Drug Products
Food and Drug Administration
5600 Fishers Lane
HFD-530
Rockville, MD 20857

RE: NDA #20-326
Neutrexin™ I.V.
Infusion (trimetrexate)

This Submission: New Drug Application (NDA)

Dear Dr. Feigal:

Enclosed please find two copies (1 archival, 1 review copy) of U.S. Bioscience's New Drug Application for Neutrexin™ I.V. Infusion (trimetrexate). As per our conference call with Dr. Mark Goldberger on January 11, 1993, the proposed indication for Neutrexin™ I.V. is as follows:

> ***Neutrexin™ I.V. Infusion (trimetrexate) with concurrent leucovorin administration (leucovorin protection) is indicated as an alternative therapy for the treatment of moderate or severe Pneumocystis carinii pneumonia in patients with acquired immunodeficiency syndrome (AIDS) who are not candidates for trimethoprim/sulfamethoxazole therapy.***

This submission consists of 109 volumes. Four additional copies of the draft labeling are appended to this letter. The summaries have been transferred to disks using WordPerfect 5.1 and will be sent directly to Mr. Isom.

In preparing this application, U.S. Bioscience has addressed all the issues discussed with the Division of Anti-Viral Drug Products at our meetings of [redacted]. Analyses requested by the FDA in their letter of March 11, 1992 have been incorporated into the Integrated Clinical and Statistical Reports. [redacted]

One Tower Bridge
100 Front Street • West Conshohocken, PA 19428
(215) 832-4505 • FAX (215) 832-4500

We appreciate the guidance the Division has provided and look forward to working together to expeditiously address any questions that arise during your review. Please contact me if I can be of any assistance. My office telephone number is (215) 832-4505 and my telefax is (215) 832-4500.

Sincerely,

Barbara Scheffler

Barbara Scheffler

Enclosures

cc:

w/125TMTX.NDA

Exhibit 8

CI NUMBER= 898 APPL NUMBER= 29,796

DOC DATE	SER/ REF #	TITLE

09-MAR-87 1 INITIAL IND

CONTENT:

VOLUMES=10

ITEM 1: DRUG NAME, STRUCTURE, AND METHOD OF ADMINISTRATION

ITEM 2: DRUG COMPONENTS OF THE FORMULATED DRUG.

ITEM 3: QUANTITATIVE COMPOSITION OF THE FORMULATED DRUG.

ITEM 4: DRUG SOURCE AND PREPARATION OF THE NEW DRUG SUBSTANCE.

ITEM 5: MANUFACTURING METHODS, FACILITIES, AND CONTROLS FOR THE FORMULATED DRUG.

ITEM 6: PRECLINICAL AND OTHER PERTINENT BACKGROUND INFORMATION.

ITEM 7: INFORMATIONAL MATERIAL TO BE SUPPLIED INVESTIGATORS AND DRUG LABEL.

ITEM 8: COMPANY REQUIREMENTS FOR CLINICAL INVESTIGATORS.

ITEM 9: NAME AND QUALIFICATIONS OF THE MONITORS AND INVESTIGATORS.

ITEM 10: PROPOSED CLINICAL INVESTIGATIONS.

09-MAR-87 1 INITIAL IND - CONTINUED

CONTENT:

ITEM 11: STATEMENT REGARDING NOTIFICATION OF THE FOOD AND DRUG ADMINISTRATION IF THE INVESTIGATION IS DISCONTINUED AND THE REASON THEREFORE.

ITEM 12: STATEMENT REGARDING NOTIFICATION OF INVESTIGATORS IF THE NEW DRUG APPLICATION IS APPROVED OR THE INVESTIGATION IS DISCONTINUED.

ITEM 13: STATEMENT REGARDING NOTIFICATION OF THE FOOD AND DRUG ADMINISTRATION IF THE INVESTIGATIONAL DRUG IS TO BE SOLD.

ITEM 14: STATEMENTS ASSURING THAT WE WILL COMPLY WITH THE 30-DAY-HOLD PERIOD PRIOR TO THE IMPLEMENTATION OF HUMAN CLINICAL TRIALS AND CLINICAL INVESTIATIONS WILL NOT BE INITIATED PRIOR TO APPROVAL OF EACH STUDY BY AN INSTITUTIONAL REVIEW BOARD.

ITEM 15: STATEMENT REGARDING ENVIRONMENTAL IMPACT ANALYSIS REPORT.

CI NUMBER= 898 APPL NUMBER= 29,796

DOC DATE	SER/ REF #	TITLE
09-MAR-87	1	INITIAL IND - CONTINUED

CONTENT:

ITEM 16: STATEMENT REGARDING GOOD LABOARATORY PRACTICE COMPLIANCE.

13-MAR-87 LETTER FROM FDA ACKNOWLEDGING RECEIPT (IND 29,796)

CONTENT:

LETTER FROM: FDA
RE: ACKNOWLEDGEMENT OF RECEIPT OF IND ON 10-MAR-87; NUMBER 29,796 ASSIGNED.

08-MAY-87 2 LETTER RE: VERBAL REQUEST FOR INFORMATION

CONTENT:

LETTER TO: TABOR, EDWARD, M.D.
RE: 30-MAR-87 TELEPHONE CONFERENCE REGARDING THE [redacted] THE LETTER CONTAINS PROPOSALS FOR [redacted]

27-MAY-87 LETTER FROM FDA RE: CLINICAL HOLD

CONTENT:

LETTER FROM: TABOR, EDWARD, M.D.
RE: [redacted] ON THIS IND:
1) REQUEST ADDITIONAL INFORMATION.
2) LIST OF RECOMMENDATIONS AND COMMENTS FOR PR. 898-34.

18-JUN-87 3 LETTER RE: CONFIRMING AGREEMENT

CONTENT:

LETTER TO: TABOR, EDWARD, M.D.
RE: CONFIRMING AGREEMENTS MADE AT 17-JUN-87 FDA MEETING:
1) [redacted]
2) [redacted]
3) [redacted]
5) [redacted]

CI NUMBER= 898 APPL NUMBER= 29,796

DOC DATE	SER/ REF #	TITLE

08-JUL-87 4 LETTER RE: RESPONSE TO REQUEST FOR INFORMATION
CONTENT:

LETTER TO: TABOR, EDWARD, M.D.
RE: RESPONSE TO 27-MAY-87 WRITTEN REQUEST FOR INFORMATION:
1) 30-JUN-87 REPORT FROM: BENDER, J., M.D.
2) RR MEMO-730-00345
AUTHOR: MACKELLAR, F.A.
DATE: 21-JUL-83
"CHEMISTRY AND MANUFACTURING AND ANALYTICAL SPECIFICATIONS FOR TRIMETREXATE"
3) 24-JUN-87 REPORT FROM: DR. ZINNES
4) 7-JUL-87 REPORT FROM: BRENNAN, S.
5) 29-JUN-87 REPORT FROM: CANIS, O.

04-AUG-87 LETTER FROM FDA RE: MINUTES OF FDA MEETING
CONTENT:

LETTER FROM: TABOR, EDWARD, M.D.
DATE: 17-JUN-87
FDA MEETING WITH NCI AND PARKE-DAVIS.

05-AUG-87 5 LETTER RE: RESPONSE TO REQUEST FOR INFORMATION
CONTENT:

LETTER TO: TABOR, EDWARD, M.D.
RE: [redacted]

REPORT BY: BOONSTRA, JOHN
DATE: 23-JUL-87

27-AUG-87 6 INFORMATION AMENDMENT
CONTENT:

RR 764-00830
AUTHOR: BULLEN, W.W. ET AL
DATE: 23-JUL-87
[redacted]

RR 764-00838
AUTHOR: WHITFIELD, L.R. ET AL
DATE: 22-JUL-87
[redacted]

CI NUMBER= 898 APPL NUMBER= 29,796

DOC DATE	SER/ REF #	TITLE

28-AUG-87 7 LETTER RE: RESPONSE TO REQUEST FOR INFORMATION
CONTENT:
LETTER TO: TABOR, EDWARD, M.D.
RE: RESPONSE TO 4-AUG-87 WRITTEN REQUEST FOR INFORMATION:
1) REPORT FROM: PEGG, G.
DATE: 27-AUG-87
ANSWERS THE PRECLINICAL TOXICOLOGY COMMENTS.
2) REPORT FROM: BENDER, J.
DATE: 27-AUG-87
RESPONDS TO THE COMMENTS CONCERNING THE CLINICAL STUDY.
3) REPORT FROM: COHEN, M.
DATE: 27-AIG-87
REGARDING THE MICROBIOLOGICAL DATA.

07-OCT-87 LETTER FROM FDA RE: PROTOCOL APPROVAL
CONTENT:
LETTER FROM: TABOR, EDWARD, M.D.
RE: [redacted]

21-OCT-87
CONTENT:
LETTER FROM: TABOR, EDWARD, M.D.
RE: [redacted]

26-OCT-87 8 LETTER RE: RESPONSE TO REQUEST FOR INFORMATION
CONTENT:
LETTER TO: TABOR, EDWARD, M.D.
RE: [redacted]

30-OCT-87 9 LETTER RE: TRANSMISSION
CONTENT:
LETTER TO: BROWDEN, NORMA J., M.D.
RE: TRANSMITTING TRIMETREXATE TOXICOLOGICAL/ PHARMACOLOGICAL SUMMARY.

CI NUMBER= 898 APPL NUMBER= 29,796

DOC DATE	SER/ REF #	TITLE
09-NOV-87	10	LETTER RE: CHEMISTRY, MANUFACTURING AND CONTROLS

CONTENT:

LETTER TO: DIVISION OF ANTI-INFECTIVE
RR X-969-00051
RE: [redacted]

11-NOV-87 11 LETTER TO: REQUEST FOR MEETING

CONTENT:

LETTER TO: TABOR, EDWARD, M.D.
RE: REQUEST MEETING TO DISCUSS PRECLINICAL TOXICOLOGY DATA FOR NDA.

22-DEC-87 12 LETTER RE: REQUEST MEETING

CONTENT:

LETTER TO: TABOR, EDWARD, M.D.
RE: [redacted]

13-JAN-88 13 LETTER RE: CHEMISTRY, MANUFACTURING AND CONTROLS

CONTENT:

LETTER TO: TABOR, EDWARD, M.D.
RR X-969-00057
RE: [redacted]

19-JAN-88 14 LETTER RE: CONFIRMATION OF MEETING

CONTENT:

LETTER TO: COOPER, ELLEN, M.D.
RE: CONFIRMING FDA MEETING TO BE HELD ON 2-FEB-88, AT 10 AM.

CI NUMBER= 898 APPL NUMBER= 29,796

DOC DATE	SER/ REF #	TITLE
03-FEB-88	15	INFORMATION AMENDMENT

CONTENT:

RR MEMO-750-00251
AUTHOR: COHEN, M.A.
DATE: 25-JAN-88
[redacted]

RR 764-00950
AUTHOR: MCNALLY, W. ET AL
DATE: 6-JAN-88
[redacted]

11-FEB-88	16	PR. 898-34 CENTERS 12, 18, 32 AND 34
11-FEB-88	17	PR. 898-37 CENTERS 9, 17 AND 35
11-FEB-88	18	PR. 898-38 CENTERS 9 AND 34
16-FEB-88	19	MINUTES OF FDA MEETING

CONTENT:

DATE: 2-FEB-88
FDA MEETING REGARDING THE FOLLOWING:
1) [redacted]
2) [redacted]

18-FEB-88	20	PR. 898-34-7
26-FEB-88	21	LETTER RE: RESPONSE TO REQUEST FOR INFORMATION

CONTENT:

LETTER TO: TRAPNELL, CAROL BRAUN, M.D.
RE: [redacted]

CI NUMBER= 898 APPL NUMBER= 29,796

DOC DATE	SER/ REF #	TITLE
26-FEB-88	22	PR. 898-34 CENTERS 26, 30, 31 AND 33
26-FEB-88	23	LETTER RE: PHYSICIAN TREATMENT IND

CONTENT:

LETTER TO: TRAPNELL, CAROL BRAUN, M.D.
RE: [redacted]

04-MAR-88	24	INFORMATION AMENDMENT

CONTENT:

RR 764-00964
AUTHOR: BULLEN, W.W. ET AL
DATE: 29-JAN-88
[redacted]

31-MAR-88	25	LETTER RE: CONFIRMATION OF MEETING

CONTENT:

LETTER TO: COOPER, ELLEN, M.D.
RE: CONFIRMING 26-APR-88 FDA MEETING AT 9 AM TO DISCUSS THE FOLLOWING:
1) [redacted]
2) [redacted]

28-APR-88	26	INFORMATION AMENDMENT

CONTENT:

RR 745-01187
AUTHOR: PEGG, D.G. ET AL
DATE: 31-MAR-88
[redacted]

CI NUMBER= 898 APPL NUMBER= 29,796

DOC DATE	SER/ REF #	TITLE
		RR 745-01212 AUTHOR: KRISHNA, G. ET AL DATE: 30-MAR-88 [redacted]
04-MAY-88	27	MINUTES OF FDA MEETING
CONTENT:		DATE: 26-APR-88 RE: FDA MEETING TO DISCUSS THE FOLLOWING: 1) [redacted] 2) [redacted]
26-MAY-88	28	LETTER RE: PERMISSION REQUEST
CONTENT:		LETTER TO: COOPER, ELLEN, M.D. RE: [redacted]
27-MAY-88	29	LETTER RE: PHYSICIAN TREATMENT IND
CONTENT:		LETTER TO: TRAPNELL, CAROL BRAUN, M.D. RE: [redacted]
07-JUN-88	30	INFORMATION AMENDMENT
CONTENT:		REVISED PAGES FOR PR. 898-37 PGS. 5, 13, 18, 22 AND 28 DATE: 7-JUN-88 REVISED PAGES FOR PR. 898-38 PGS. 5, 7, 8, 11, 12, 14, 16, 19 AND 25 DATE: 7-JUN-88

CI NUMBER= 898 APPL NUMBER= 29,796

DOC DATE	SER/ REF #	TITLE
15-JUN-88	31	LETTER RE: REQUEST FOR INFORMATION

CONTENT:

LETTER TO: COOPER, ELLEN
PRS. 898-37 AND 898-38
RE: [redacted]

20-JUN-88	32	LETTER RE: PHYSICIAN TREATMENT IND

CONTENT:

LETTER TO: TRAPNELL, CAROL
RE: [redacted]

20-JUN-88	33	INFORMATION AMENDMENT

CONTENT:

RR 745-01247
AUTHOR: PEGG, D.G. ET AL
DATE: 25-MAY-88
[redacted]

27-JUN-88	34	PR. 898-38-63
27-JUN-88	35	PR. 898-37-2
06-JUL-88	36	LETTER RE: PHYSICIAN TREATMENT IND

CONTENT:

LETTER TO: TRAPNELL, CAROL, M.D.
RE: [redacted]

06-JUL-88	37	PR. 898-37 CENTERS 5, 12 AND 34

CI NUMBER= 898 APPL NUMBER= 29,796

DOC DATE	SER/ REF #	TITLE
06-JUL-88	38	PR. 898-38 CENTERS 2, 5, 12 AND 34
11-JUL-88		LETTER FROM FDA RE: CONFIRMATION OF REQUEST

CONTENT:
LETTER FROM: COOPER, ELLEN, M.D.
RE: CONFIRMING APPROVAL FOR THE CLINCIAL STUDIES OF PRS. 898-37 AND 898-38 TO PROCEED.

12-JUL-88	39	PR. 898-37 CENTERS 23, 25, 31, 32, 45, 51 AND 59
12-JUL-88	40	PR. 898-38 CENTERS 23, 25, 31, 45, 51 AND 59
20-JUL-88	41	PR. 898-37 CENTERS 10 AND 63/INFORMATION AMENDMENT

CONTENT:
RR 764-01037
AUTHOR: JOHNSON, E.L. ET AL
DATE: 30-JUN-88
[redacted]

20-JUL-88	42	PR. 898-38-10
20-JUL-88	43	LETTER RE: PHYSICIAN TREATMENT IND

CONTENT:
LETTER TO: TRAPNELL, CAROL, M.D.
RE: [redacted]

20-JUL-88	44	LETTER RE: PHYSICIAN TREATMENT IND

CONTENT:
LETTER TO: TRAPNELL, CAROL, M.D.
RE: [redacted]

CI NUMBER= 898 APPL NUMBER= 29,796

DOC DATE	SER/ REF #	TITLE
21-JUL-88	45	LETTER RE: PHYSICIAN TREATMENT IND

CONTENT:

LETTER TO: TRAPNELL, CAROL, M.D.
RE: [redacted]

PHYSICIAN TREATMENT IND 31,722

28-JUL-88	46	PR. 898-37 CENTERS 17, 38, 43, 54 AND 58
28-JUL-88	47	PR. 898-38 CENTERS 17, 33, 38, 43 AND 58/PR. 898-40-4
04-AUG-88	48	PR. 898-37 CENTERS 7, 27 AND 47
04-AUG-88	49	PR. 898-38 CENTERS 7 AND 27/PR. 898-40-1
09-AUG-88	50	LETTER RE: VERBAL REQUEST FOR INFORMATION

CONTENT:

LETTER TO: DIVISION OF ANTI-VIRAL
RE: FDA REQUESTED LIST OF INVESTIGATORS AND THEIR INSTITUTIONS WHO WILL PARTICIPATE IN EITHER ONE OR BOTH OF PR. 898-37 AND 898-38.

11-AUG-88	51	PR. 898-37-9, 898-38 CENTERS 9 AND 57
11-AUG-88	52	LETTER RE: PHYSICIAN TREATMENT IND

CONTENT:

LETTER TO: TRAPNELL, CAROL, M.D.
RE: [redacted]

CI NUMBER= 898 APPL NUMBER= 29,796

DOC DATE	SER/ REF #	TITLE
18-AUG-88	53	LETTER PHYSICIAN TREATMENT IND

CONTENT:

LETTER TO: TRAPNELL, CAROL, M.D.
RE:

1) [redacted]

2) [redacted]

18-AUG-88	54	PR. 898-37-6
18-AUG-88	55	PR. 898-37 CENTERS 44, 46 AND 64
18-AUG-88	56	PR. 898-38 CENTERS 39 AND 46
18-AUG-88	57	PR. 898-39 CENTERS 1, 2, 3 AND 4
18-AUG-88	58	LETTER RE: INFORMATION

CONTENT:

LETTER TO: BONA, D.
RE: [redacted]

01-SEP-88	59	PR. 898-37 CENTERS 41 AND 48/PR. 898-38-48
01-SEP-88	60	NEW SUB-INVESTIGATORS

CONTENT:

PRS. 898-37-23 AND 898-38-23
BOOMSMA, JOAN, M.D.
URBAN, MONICA, M.D.

Pr. 898-40-1.
GIRARD, P.M., M.D.

CI NUMBER= 898 APPL NUMBER= 29,796

DOC DATE	SER/ REF #	TITLE
01-SEP-88	61	LETTER RE: PHYSICIAN TREATMENT INDS

CONTENT:

LETTER TO: TRAPNELL, CAROL, M.D.
RE: [redacted]

1) [redacted]

2) [redacted]

01-SEP-88	62	INFORMATION AMENDMENT

CONTENT:

RR 745-01250
AUTHOR: KRISHNA, G. ET AL
DATE: 2-AUG-88
[redacted]

08-SEP-88	63	PR. 898-37 CENTERS 1 AND 60
08-SEP-88	64	PR. 898-38 CENTERS 1 AND 60/PR. 898-39-8
22-SEP-88	65	LETTER RE: PHYSICIAN TREATMENT IND

CONTENT:

LETTER TO: TRAPNELL, CAROL, M.D.
RE: [redacted]

22-SEP-88	66	PRS. 898-37-36 AND 898-38-36
22-SEP-88	67	IB UPDATE

CONTENT:

DATE: 22-AUG-88
RR X-720-02456
AUTHORS: BENDER, J.F.
GMEREK, D.E.

CI NUMBER= 898 APPL NUMBER= 29,796

DOC DATE	SER/ REF #	TITLE
29-SEP-88	68	PR. 898-37 CENTERS 8 AND 26/PR. 898-38-26
29-SEP-88	69	INFORMATION AMENDMENT

CONTENT:

RR 764-01042
AUTHOR: BULLEN, W.W. ET AL
DATE: 14-JUL-88
[redacted]

29-SEP-88	70	PR. 898-39-5
13-OCT-88	71	LETTER RE: PHYSICIAN TREATMENT IND

CONTENT:

LETTER TO: TRAPNELL, CAROL, M.D.
RE: [redacted]

13-OCT-88	72	PRS. 898-39-10 AND 898-40-2
20-OCT-88	73	PR. 898-39 CENTERS 6 AND 7/PR. 898-40-3
28-OCT-88		LETTER RE: PRE-NDA

CONTENT:

LETTER TO: HOYLE, PETER, PH.D.
RE: [redacted]

10-NOV-88	74	PR. 898-40-5/NEW SUB-INVESTIGATOR

CONTENT:

PRS. 898-37-25 AND 898-38-25
CRENNA, JOAN, M.D.

CI NUMBER= 898 APPL NUMBER= 29,796

DOC DATE	SER/ REF #	TITLE
10-NOV-88	75	LETTER RE: PHYSICIAN TREATMENT IND

CONTENT:

LETTER TO: TRAPNELL, CAROL, M.D.
RE: [redacted]

16-NOV-88	76	SAFETY REPORT

CONTENT:

PATIENT NO.: 1 (STS)
PR. 898-37-23
AE: GRAND MAL SEIZURE
AE 001-0898-880006-00

01-DEC-88	77	PR. 898-37-65
01-DEC-88	78	INFORMATION AMENDMENT/IB UPDATE

CONTENT:

RR 250-01551
AUTHOR: HOUSTON, B.J. ET AL
DATE: 1-NOV-88
[redacted]

REVISED PAGES RR-X-720-02456(IB)
PGS. 3 AND 4
DATE: 11-NOV-88

07-DEC-88	79	LETTER RE: DISCONTINUANCE OF ENROLLMENT

CONTENT:

LETTER TO: DIVISION OF ANTI-VIRAL
RE: [redacted]

CI NUMBER= 898 APPL NUMBER= 29,796

DOC DATE	SER/ REF #	TITLE
12-JAN-89	80	SAFETY REPORT

CONTENT:

PATIENT NO.: 2 (MT)
PR. 898-39-4
AE: SEVERE HYPONATREMIA
AE 044-0898-880003-00

DOC DATE	SER/ REF #	TITLE
31-JAN-89	81	LETTER RE: PHYSICIAN TREATMENT IND

CONTENT:

LETTER TO: TRAPNELL, CAROL, M.D.
RE:

1) [redacted]

2) [redacted]

DOC DATE	SER/ REF #	TITLE
31-JAN-89	82	INFORMATION AMENDMENT

CONTENT:

RR 764-01055
AUTHOR: ANDRESS, L.D. ET AL
DATE: 22-DEC-88

[redacted]

DOC DATE	SER/ REF #	TITLE
10-MAR-89	83	LETTER RE: PHYSICIAN TREATMENT IND

CONTENT:

LETTER TO: TRAPNELL, CAROL, M.D.
RE: [redacted]

PHYSICIAN TREATMENT IND 23,739

CI NUMBER= 898 APPL NUMBER= 29,796

DOC DATE	SER/ REF #	TITLE
03-APR-89	84	INFORMATION AMENDMENT

CONTENT:

RR 764-01147
AUTHOR: WONG, B. ET AL
DATE: 21-FEB-89
[redacted]

31-MAY-89	85	LETTER RE: PHYSICIAN TREATMENT IND

CONTENT:

LETTER TO: TRAPNELL, CAROL, M.D.
RE: [redacted]

1) [redacted]

2) [redacted]

20-JUN-89	86	LETTER RE: PHYSICIAN TREATMENT IND

CONTENT:

LETTER TO: TRAPNELL, CAROL, M.D.
RE: [redacted]

09-AUG-89	87	LETTER RE: PHYSICIAN TREATMENT IND

CONTENT:

LETTER TO: TRAPNELL, CAROL, M.D.
RE: [redacted]

29-AUG-89	88	LETTER RE: PHYSICIAN TREATMENT IND

CONTENT:

LETTER TO: TRAPNELL, CAROL, M.D.
RE: [redacted]

CI NUMBER= 898 APPL NUMBER= 29,796

DOC DATE	SER/ REF #	TITLE
12-SEP-89	89	LETTER RE: PHYSICIAN TREATMENT IND

CONTENT:

LETTER TO: TRAPNELL, CAROL, M.D.
RE: [redacted]

12-SEP-89	90	INFORMATION AMENDMENT

CONTENT:

RR 745-01346
AUTHOR: MACDONALD, J.R.
DATE: 7-AUG-89
[redacted]

20-SEP-89	91	ANNUAL REPORT

CONTENT:

ISSUE DATE: 18-SEP-89

02-OCT-89	92	LETTER RE: PHYSICIAN TREATMENT IND

CONTENT:

LETTER TO: TRAPNELL, CAROL, M.D.
RE: [redacted]

04-OCT-89		MEMO RE: REQUEST FOR INFORMATION

CONTENT:

MEMO RE: FDA QUERY REGARDING TOXICOLOGY REPORT.
CROSS REFERENCE: SERIAL #90

09-OCT-89	93	INFORMATION AMENDMENT

CONTENT:

RR 745-01356
AUTHOR: GRAZIANO, M.J.
DATE: 8-SEP-89
[redacted]

CI NUMBER= 898 APPL NUMBER= 29,796

DOC DATE	SER/ REF #	TITLE
09-OCT-89	94	LETTER RE: PHYSICIAN TREATMENT IND

CONTENT:

LETTER TO: TRAPNELL, CAROL, M.D.
RE: [redacted]

16-NOV-89	95	LETTER RE: PHYSICIAN TREATMENT IND

CONTENT:

LETTER TO: TRAPNELL, CAROL, M.D.
RE: [redacted]

06-DEC-89		LETTER FROM FDA: REQUEST FOR INFORMATION

CONTENT:

LETTER FROM: WYKOFF, RANDOLPH F.
RE: HOPE ACT FOR AIDS TREATMENT

15-DEC-89	96	LETTER RE: PHYSICIAN TREATMENT IND

CONTENT:

LETTER TO: TRAPNELL, CAROL, M.D.
RE: [redacted]

04-JAN-90	97	LETTER RE: PHYSICIAN TREATMENT IND

CONTENT:

LETTER TO: TRAPNELL, CAROL, M.D.
RE: [redacted]

CI NUMBER= 898 APPL NUMBER= 29,796

DOC DATE	SER/ REF #	TITLE
04-JAN-90	98	LETTER RE: PHYSICIAN TREATMENT IND

CONTENT:

LETTER TO: TRAPNELL, CAROL, M.D.
RE: [redacted]

29-JAN-90	99	INFORMATION AMENDMENT

CONTENT:

RR MEMO-745-01548
AUTHOR: MACDONALD, J.R.
DATE: 15-DEC-89
[redacted]

RR MEMO-250-01522
AUTHOR: HOUSTON, B.J.
DATE: 8-DEC-89
[redacted]

05-FEB-90	100	LETTER RE: PHYSICIAN TREATMENT IND

CONTENT:

LETTER TO: TRAPNELL, CAROL, M.D.
RE: [redacted]

06-FEB-90	101	LETTER RE: PHYSICIAN TREATMENT IND

CONTENT:

LETTER TO: TRAPNELL, CAROL, M.D.
RE: [redacted]

CI NUMBER= 898 APPL NUMBER= 29,796

DOC DATE	SER/ REF #	TITLE
12-MAR-90	102	LETTER RE: PHYSICIAN TREATMENT IND

CONTENT:

LETTER TO: TRAPNELL, CAROL, M.D.
RE: [redacted]

12-MAR-90	103	INFORMATION AMENDMENT

CONTENT:

RR MEMO-745-01544
AUTHOR: DETHLOFF, L.A.
DATE: 2-JAN-90
[redacted]

12-MAR-90	104	LETTER RE: PHYSICIAN TREATMENT IND

CONTENT:

LETTER TO: TRAPNELL, CAROL, M.D.
RE: [redacted]

03-MAY-90	105	LETTER RE: PHYSICIAN TREATMENT IND

CONTENT:

LETTER TO: TRAPNELL, CAROL, M.D.
RE: [redacted]

31-MAY-90	106	LETTER RE: PHYSICIAN'S TREATMENT IND

CONTENT:

LETTER TO: COOPER, ELLEN MD
CI-898
RE: [redacted]

CI NUMBER= 898 APPL NUMBER= 29,796

DOC DATE	SER/ REF #	TITLE
12-JUN-90	107	LETTER RE: PHYSICIAN'S TREATMENT IND

CONTENT:

LETTER TO: COOPER, ELLEN MD
CI-898
RE: [redacted]

28-JUN-90	108	LETTER RE: PHYSICIAN'S TREATMENT IND

CONTENT:

CI-898
RE: [redacted]

27-JUL-90	109	LETTER RE: PHYSICIAN'S TREATMENT IND

CONTENT:

LETTER TO: COOPER, ELLEN, M.D.
RE: [redacted]

11-SEP-90	110	LETTER RE: PHYSICIAN'S TREATMENT IND

CONTENT:

LETTER TO: COOPER, ELLEN, C., M.D.
RE: [redacted]

13-SEP-90	111	ANNUAL REPORT

CONTENT:

ISSUE DATE: 13-SEP-90

CI NUMBER= 898 APPL NUMBER= 29,796

DOC DATE	SER/ REF #	TITLE
20-SEP-90	112	LETTER RE: PHYSICIAN'S TREATMENT IND

CONTENT:

LETTER TO: COOPER, ELLEN, M.D.
RE: [redacted]

23-OCT-90	113	INFORMATION AMENDMENT

CONTENT:

RR 745-01637
AUTHOR: THEISS, J.C.
DATE: 24-AUG-90
[redacted]

11-APR-91	114	LETTER RE: PHYSICIAN'S TREATMENT IND

CONTENT:

LETTER TO: PECK, CARL C. M.D.
RE: [redacted]

18-APR-91	115	LETTER RE: PHYSICIAN'S TREATMENT IND

CONTENT:

LETTER TO: PECK, CARL C. M.D.
RE: [redacted]

CI NUMBER= 898 APPL NUMBER= 29,796

DOC DATE	SER/ REF #	TITLE
09-AUG-91	116	ANNUAL REPORT

CONTENT:

ISSUE DATE: 30-JUL-91

28-AUG-91 LETTER RE: LICENSING AGREEMENT

CONTENT:

LETTER TO: SCHEFFLER, BARBARA
LETTER FROM: MEYER, JULIA
RE: [redacted]

28-AUG-91 117 LETTER RE: PHYSICIAN TREATMENT IND

CONTENT:

LETTER TO: PECK, CARL M.D.
RE: [redacted]

CI NUMBER= 898 APPL NUMBER= 29,796

DOC DATE	SER/ REF #	TITLE
28-AUG-91	118	LETTER RE: PHYSICIAN'S TREATMENT IND

CONTENT:

LETTER TO: PECK, CARL MD
LETTER FROM: HOLDEN, HOWARD
RE: [redacted]

04-SEP-91		LETTER RE: CASE REPORT FORMS

CONTENT:

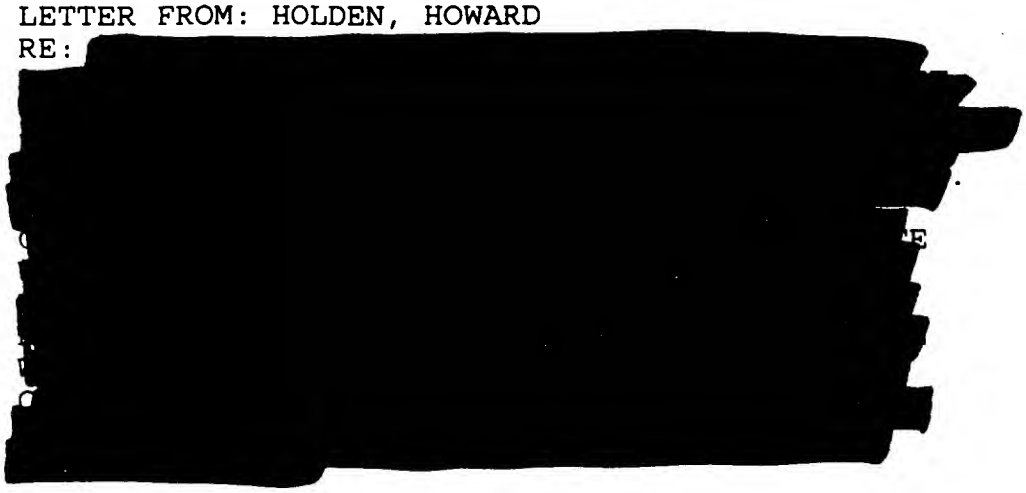
LETTER TO: SCHEFFLER, BARBARA
LETTER FROM: MEYER, JULIA
RE: [redacted]

CI NUMBER= 898 APPL NUMBER= 29,796

DOC DATE	SER/ REF #	TITLE
13-NOV-91	119	LETTER RE: TRANSFER OF IND

CONTENT:

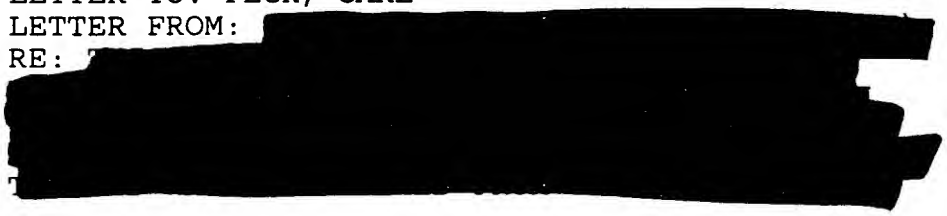
LETTER TO: PECK, CARL M.D.
LETTER FROM: HOLDEN, HOWARD
RE: [redacted]



15-NOV-91 LETTER RE: ACCEPTANCE OF IND

CONTENT:

LETTER TO: PECK, CARL
LETTER FROM: [redacted]
RE: [redacted]



07-AUG-92 128 ANNUAL REPORT (BIOSCIENCE)

CONTENT:

PERIOD COVERED: 9-JUN-91 TO 8-JUN-92
DURING THIS INTERVAL P-D TRANSFERRED IND 29,796 TO US BIOSCIENCE, INC (SN 119-123).

20-AUG-92 LETTER TO BIOSCIENCE RE: MISSING PAGES (TOX)

NEUTREXIN™ IND LOG

November 13, 1991	Letter to FDA notifying them that Parke-Davis has transferred all rights to IND #29,796 and has licensed this compound to U.S. Bioscience.
November 15, 1991	Letter informing FDA of U.S. Bioscience's acceptance of IND #29,796 for the treatment of PCP in AIDS patients from Parke-Davis Pharmaceutical Research.
November 22, 1991	USB requests Pre-NDA Submission Meeting with FDA.
January 7, 1992	USB provided FDA information regarding IND transfer.
February 7, 1992	USB provided FDA information regarding references to a publication about trimetrexate.
February 27, 1992	Pre-NDA submission meeting with FDA regarding clinical information.
March 11, 1992	Request to FDA that all rights for Orphan Drug status, which were granted to Parke-Davis, be transferred to U.S. Bioscience.
March 16, 1992	FDA approves transfer of Orphan Drug Designations to USB.
May 27, 1992	Submission of clinical protocol TMTX-C010 to FDA.
August 18, 1992	Pre-NDA meeting with FDA to discuss chemistry and manufacturing information.
November 24, 1992	USB submits summary of meetings held February 27, 1992 and August 18, 1992.
December 18, 1992	Submission of draft clinical protocol TMTX-0009.
January 11, 1993	Submitted proposed indication for trimetrexate for NDA.

NEUTREXIN™ NDA LOG

February 1, 1993	SUBMISSION OF NEUTREXIN™ (trimetrexate glucuronate for injection) NDA #20,326 TO FDA
February 2, 1993	Letter to FDA requesting a joint review by the FDA and the Canadian Health Protection Branch (HPB) of NDA #20,326.
February 15, 1993	Provided FDA clinical information.
February 22, 1993	Provided FDA clinical information.
March 1, 1993	Provided HPB with case report forms.
March 16, 1993	Provided HPB and FDA with clinical information.
March 17, 1993	Submitted Product Monograph to HPB in Canada.
March 18, 1993	Provided FDA with additional statistical data on disk.
April 1, 1993	Provided FDA microbiological information.
April 12, 1993	Submission of clinical protocols TMTX-0014 and TMTX-0015 to FDA.
April 21, 1993	Response to clinical questions from FDA.
April 28, 1993	Provided FDA with chemistry and manufacturing information.
April 28, 1993	Provided HPB with CRFs for clinical protocol TMTX-9005.
May 19, 1993	Provided FDA with Methods Validation package.
June 2, 1993	Submission of clinical protocol TMTX-C502 to FDA. U.S. Bioscience announces the availability of trimetrexate under Treatment IND.
June 26, 1993	Provided FDA with chemistry and manufacturing information.
June 29, 1993	Provided FDA with clinical information.
August 18, 1993	Provided FDA with chemistry and manufacturing information.

September 3, 1993	Provided Canada with chemistry and manufacturing information and cross-referenced.
October 15, 1993	Draft labeling and post-marketing commitments submitted to FDA.
October 18, 1993	Provided FDA with chemistry and manufacturing information.
October 28, 1993	Submission to FDA of drug product information and standard Letter of Disbarment.
November 30, 1993	Labels and information for each packaging configuration submitted to FDA.
December 3, 1993	Submitted to FDA two chemistry and manufacturing reports.
December 17, 1993	FDA approval letter for NDA #20,326 received, granting permission for commercial marketing pursuant to Section 505(c)(1)(A) of the Federal Food, Drug and Cosmetic Act.
December 24, 1993	USB receives Notice of Compliance from HPB in Canada.